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THE LARGE PERSONAL FACTOR IN BLOOD PRESSURE DETERMINATIONS BY THE OSCILLATORY METHOD *

EUGENE S. KILGORE
SAN FRANCISCO

I

The following letter, which explains itself, was sent to Drs. R. C. Cabot, W. B. Cannon, Joseph Erlanger, A. W. Hewlett, Theodore C. Janeway, Yandell Henderson, A. D. Hirschfelder, H. C. Moffitt and R. L. Wilbur.

In a series of functional heart tests recently undertaken in the Students' Infirmary upon students entering the University of California a large number of determinations of blood pressure were made. Since graphic records were desired, the Erlanger blood pressure apparatus was used; and while it was writing on the smoked surface a record of the pressure oscillations in the cuff, a float in a large U-tube of mercury was writing on the same surface a continuous record of the actual amount of pressure in the cuff as it was gradually falling. (Fragments of these manometric tracings will be noticed in the photographs I am sending you.)

In reading the results I was puzzled in quite a large number of cases to know just what instant to choose (on the pressure oscillation records) for calculating the systolic pressure (on the mercury record). Dr. R. C. Cabot, Dr. H. C. Moffitt and Dr. R. L. Wilbur were so good as to examine the records, but in the doubtful cases they did not help me to see more clearly where the systolic pressures should be read.

It therefore seemed that, in view of the number of these to us doubtful cases, and in view of the wide reputation enjoyed by the graphic oscillatory method (which undoubtedly has its best representative in Professor Erlanger's apparatus) as the most accurate for determining human blood pressures, there would be value in a comparison of the readings made independently by several different observers on the same records.

Accordingly, 100 records from eleven individuals were picked at random from a pile of about 1,300 records of 130 individuals — most all of them healthy freshmen entering college. The smoked sheets were folded together so as to expose only the oscillation records; the latter were numbered from 1 to 100, were photographed and several prints made from each plate. One set of these photographs I am mailing to you, and the others to several other clinicians and physiologists in different parts of the country. If discrepancies occur in their readings they can be expressed in millimeters of mercury by reference to the original tracings.

* From the Department of Medicine and the Students' Infirmary, University of California.

Would it be asking too much for me to request your readings on these records? If you are willing to put yourself to this trouble, will you kindly:

(1) Imagine yourself using the Erlanger apparatus in the ordinary way and watching the record of pressure oscillations being written as the air is gradually escaping from the cuff system and the pressure in the cuff approaches systolic pressure. Prick with a pin the oscillation written at the instant when you would read the mercury column for systolic pressure if the manometer were before you.

(2) Do the same for diastolic pressure. In this way mark systolic and diastolic points on each of the 100 records which you consider satisfactory ones; and if for any reason you do not give your readings on all of them, refer to them by number and give reasons for not marking them.

(3) Return the records and state what criteria you have used in marking systolic and diastolic pressures.

(4) Let me know whether you are willing (if the results should prove valuable) for your name to be published as one of a group to whom these records were submitted to be marked, without indicating which were your marks.

Drs. Cannon, Erlanger, Hewlett, Hirschfelder, Moffitt and Wilbur returned the photographs with their marks; and these marks have all been transferred to the original photographic negatives which are herewith reproduced in Figures 1 to 6. Connected with each mark is a letter (arbitrarily assigned), which represents the one who chose that point for his reading, and a number, which shows in millimeters the displacement of mercury in the U-tube at the instant when this point was written. These numbers were obtained by reference to the original drum records, which contain tracings of a float in the mercury U-tube, together with its base line and, at the beginning and end of each record, stationary marks. The manometer record was measured from the midpoint of its oscillations.

It is not to be expected that every tracing taken would be suitable for reading. Rhythmic variations in the pressure, movements of the subject's arm or other accidents frequently spoil them. Such is the case with a number among this hundred; and, following the suggestion in the letter, most of those who responded made criticisms of individual tracings. Every tracing so criticized is marked "f. r." (faulty record) following the letter which indicates the observer who made the criticism. This abbreviation is placed in the upper left hand corner if the criticism refers to the part of the record from which systolic pressure is to be determined, and in the upper right hand corner if it refers to the "diastolic part" of the tracing. In the same way, a question mark is used to indicate that doubt was expressed about the reading without criticizing the tracing; and a zero means that no mark was made. In some cases the question was inferred from the presence of two marks for systolic or diastolic readings. Failure to mark individual records in some cases seems intentional on account of doubt about where to put the marks; in other cases it seems to have been due to oversight.

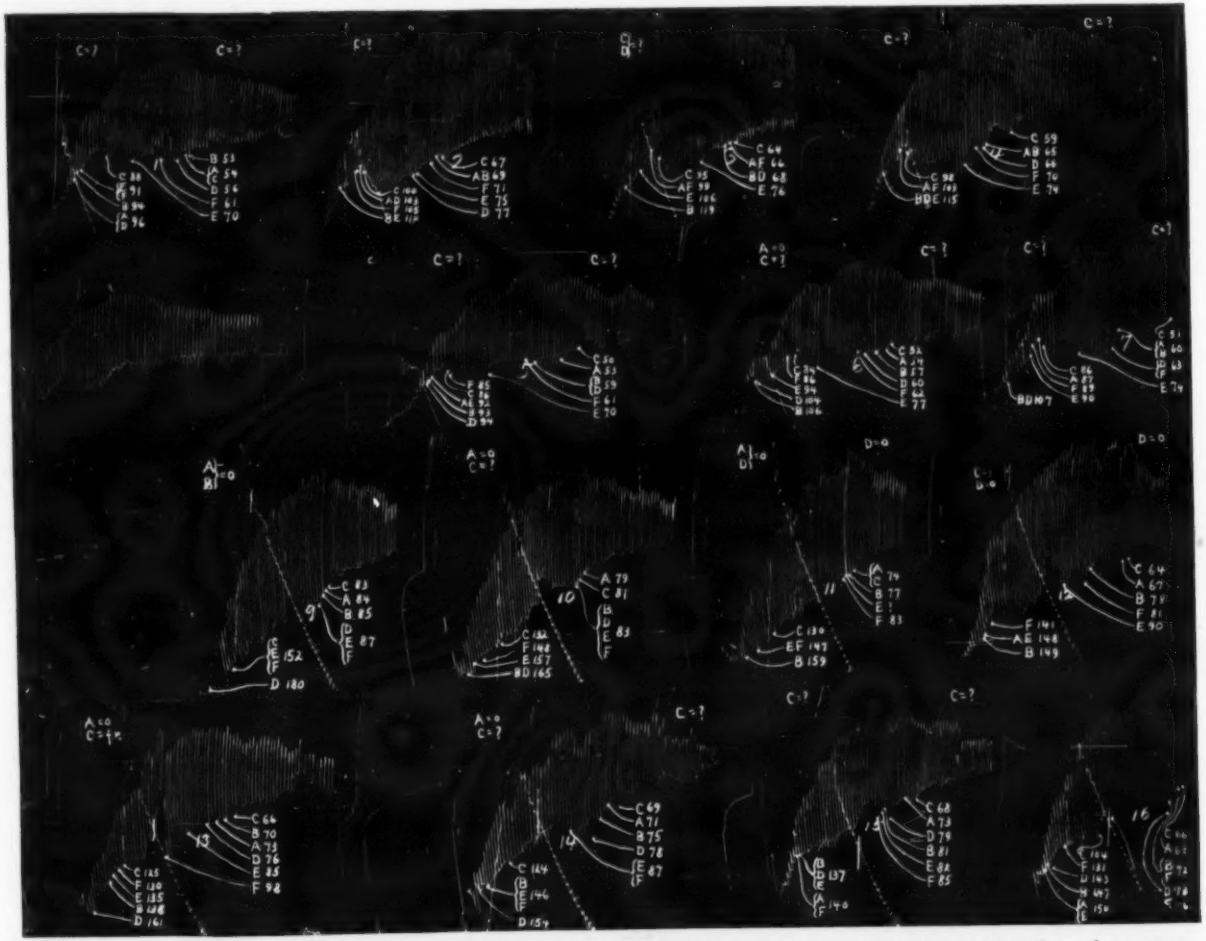

Fig. 1.—Oscillatory tracings variously marked by six individuals. Nos. 1-7, 9-16; 29 per cent. reduction (i. e., these reproductions are 71/100 as large as the original tracings).

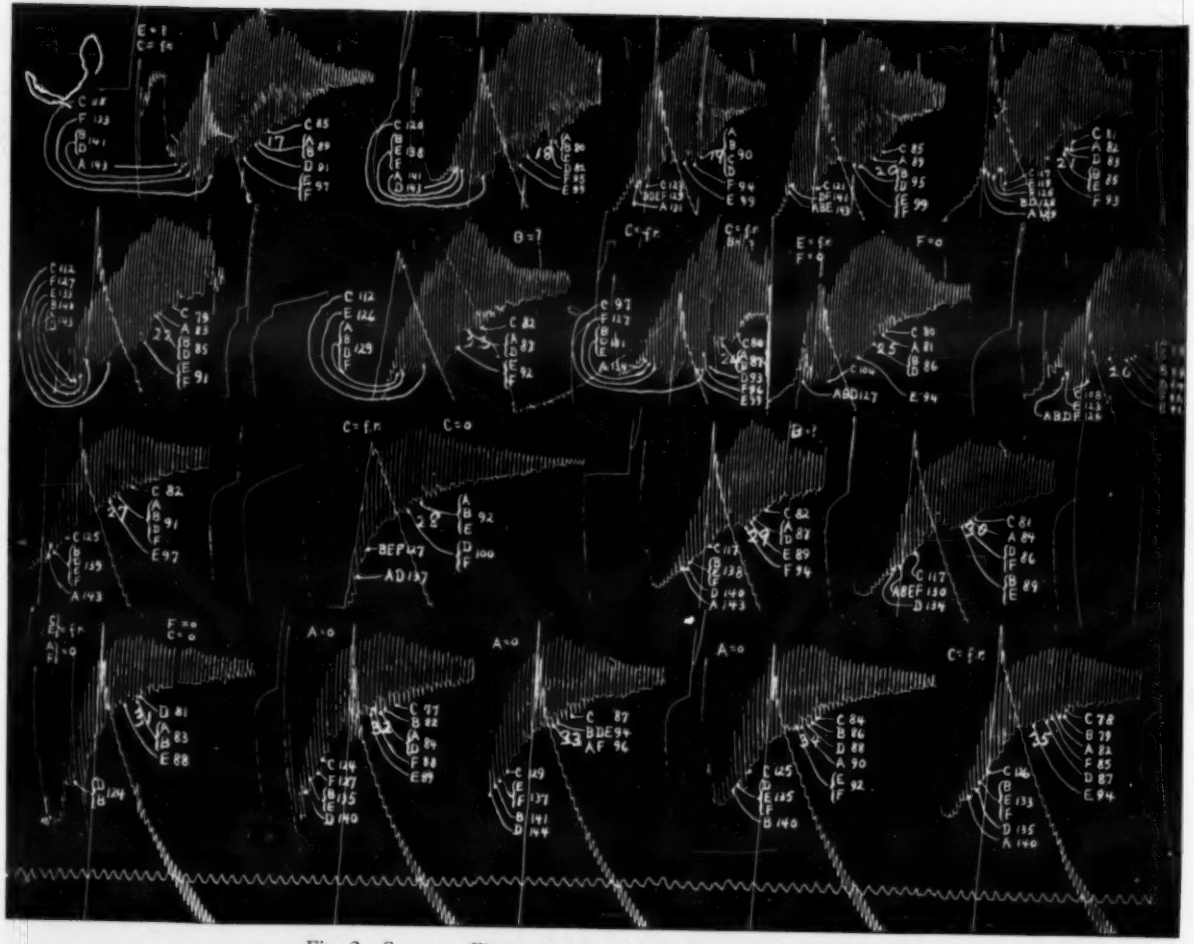

Fig. 2.—Same as Figure 1; Nos. 17-35; 29 per cent. reduction.

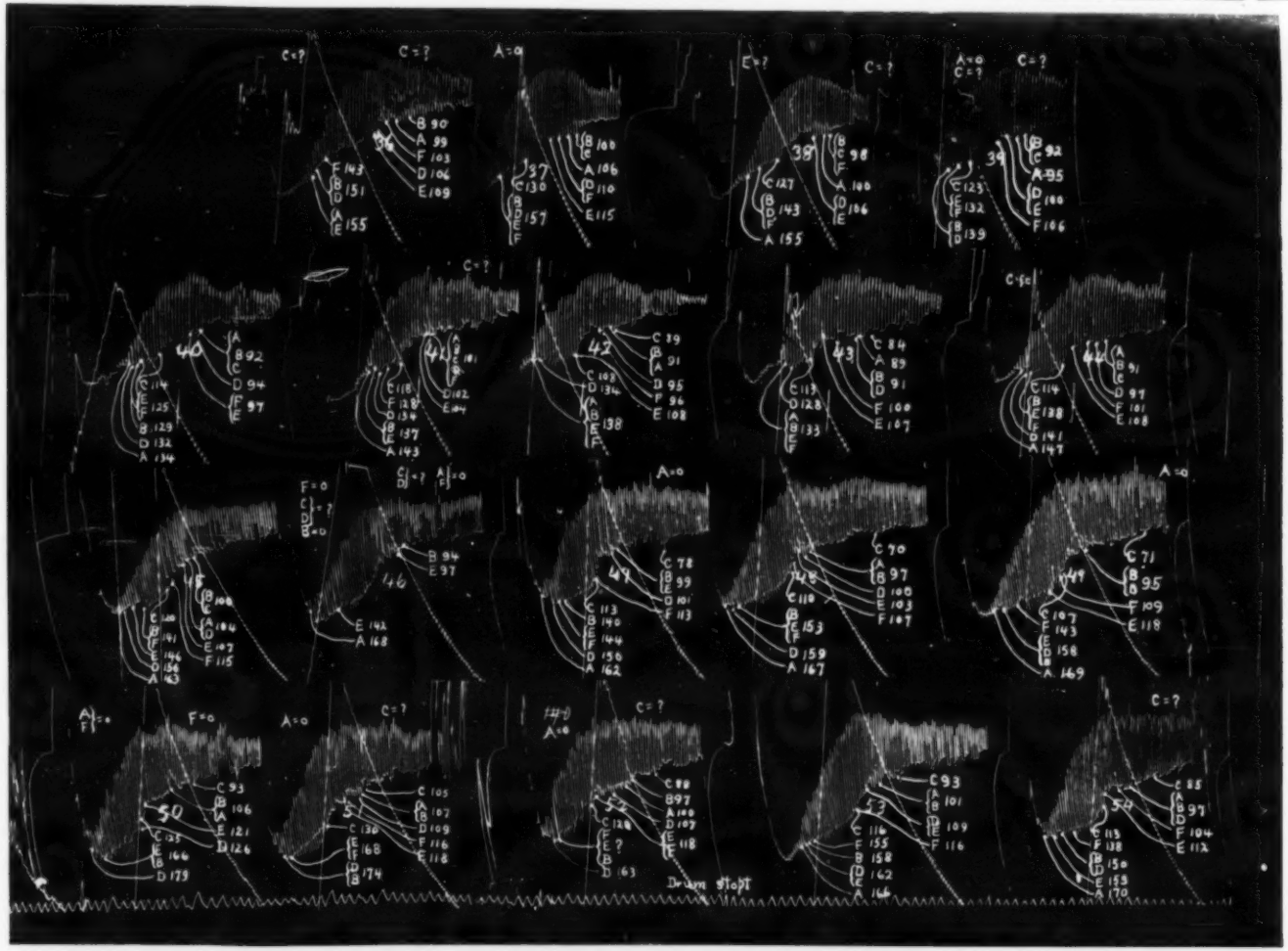

Fig. 3.—Same as Figure 1; Nos. 36-54; 26 per cent. reduction.

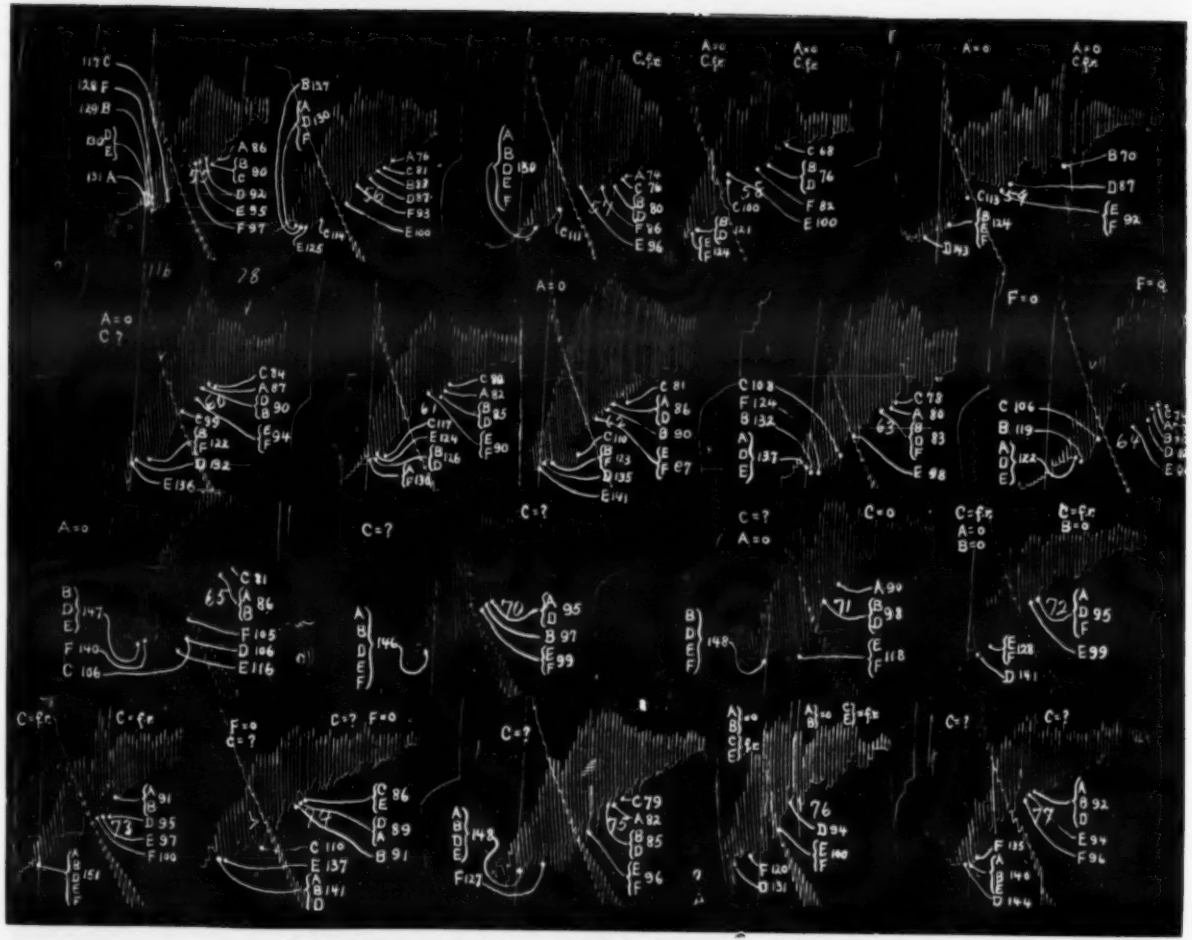

Fig. 4.—Same as Figure 1; Nos. 55-65, 70-77; 21 per cent. reduction.

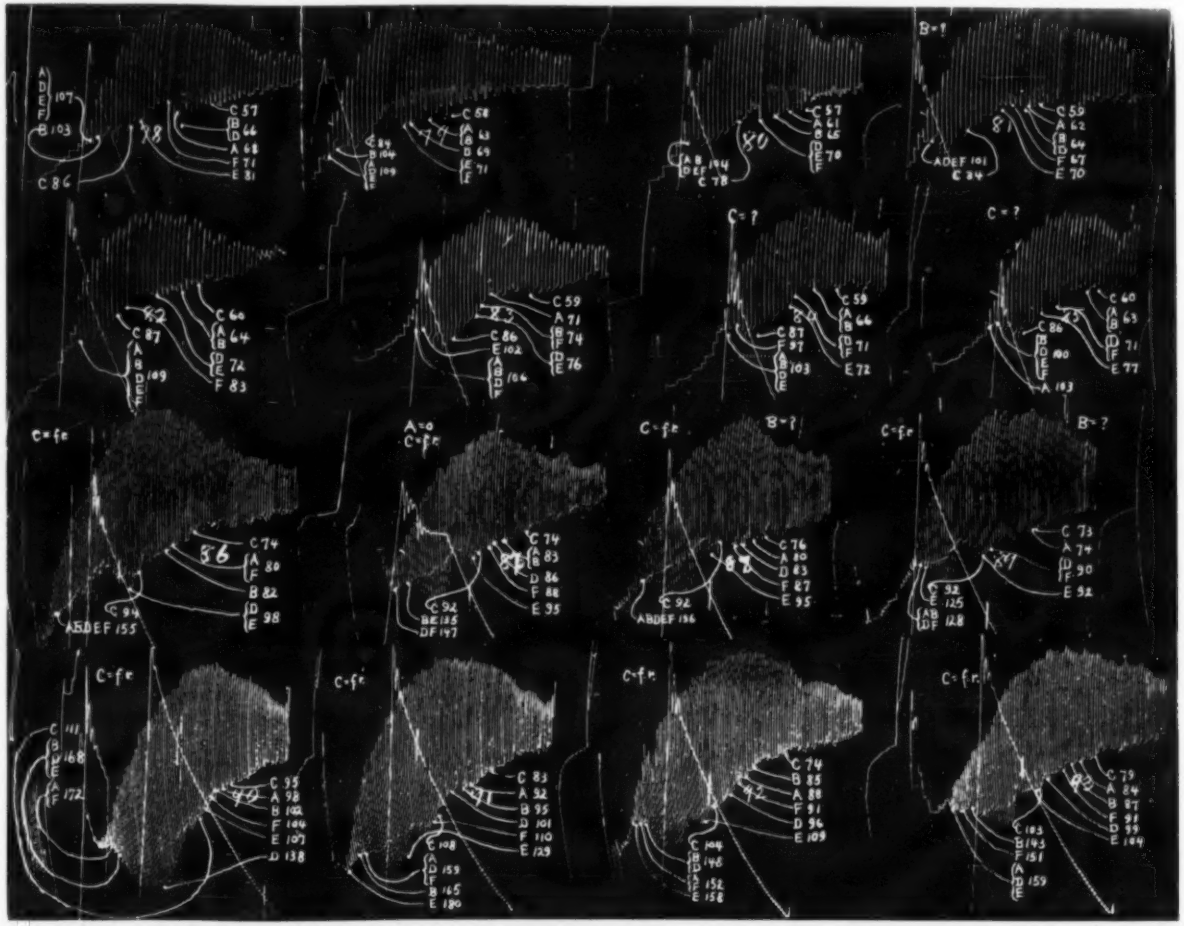

Fig. 5.—Same as Figure 1; Nos. 78-93; 24 per cent. reduction.

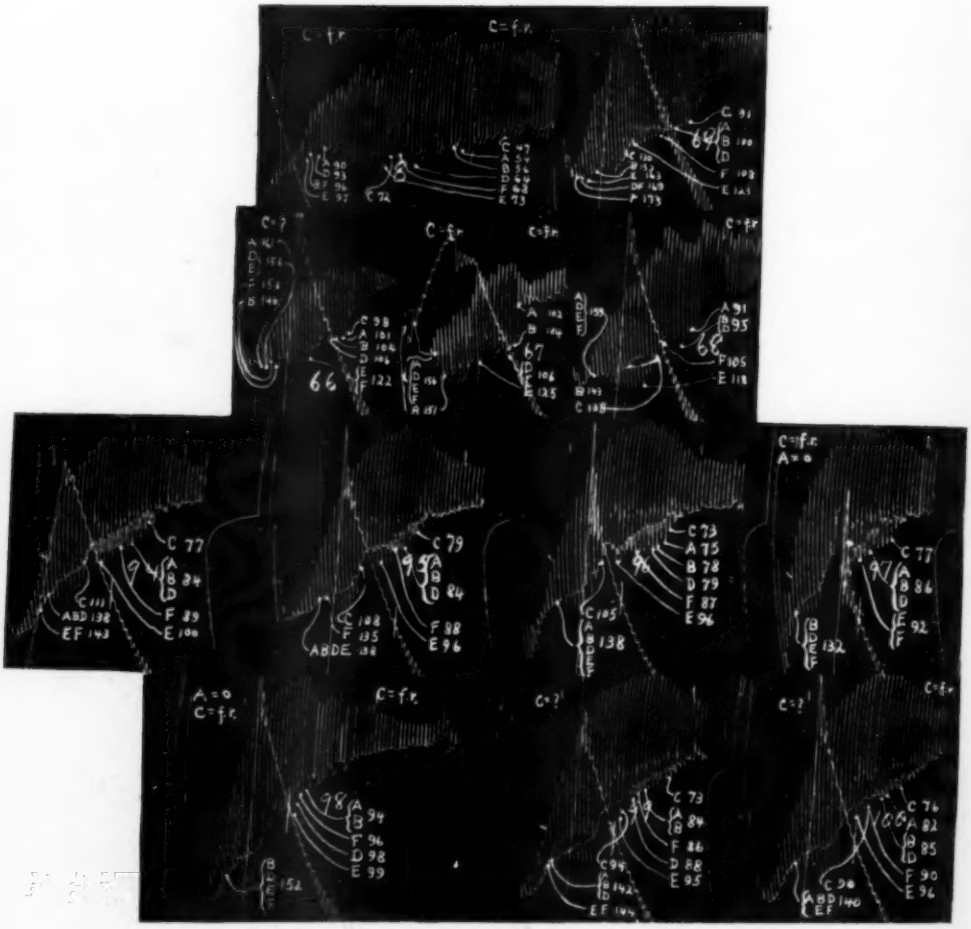

Fig. 6.—Same as Figure 1; Nos. 8, 66-69, 94-100; 17 per cent. reduction.

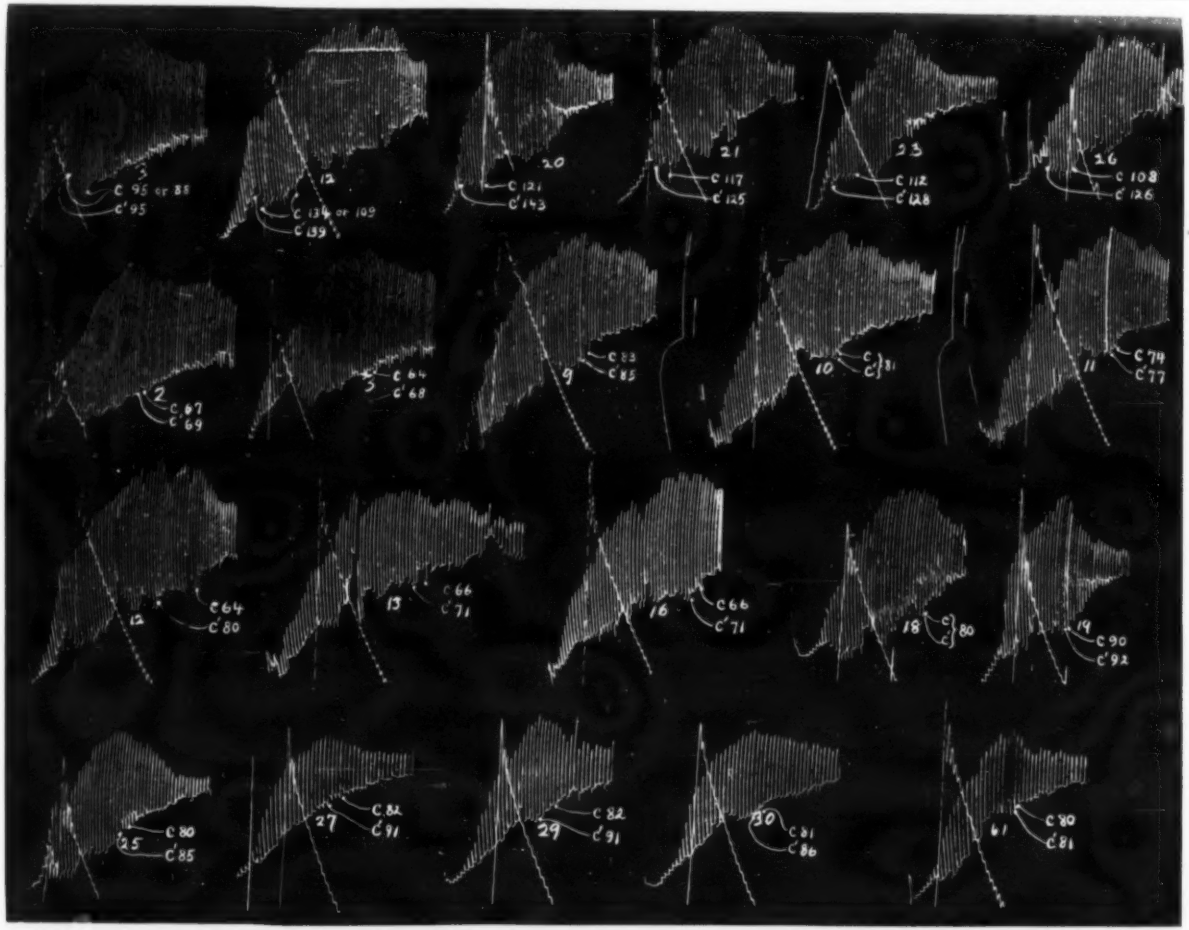

Fig. 7.—Oscillatory tracings marked at two different times by the same individual. C = marks made in 1912; C' = marks made in 1913. Upper row, systolic readings; three lower rows, diastolic readings; 29 per cent. reduction.

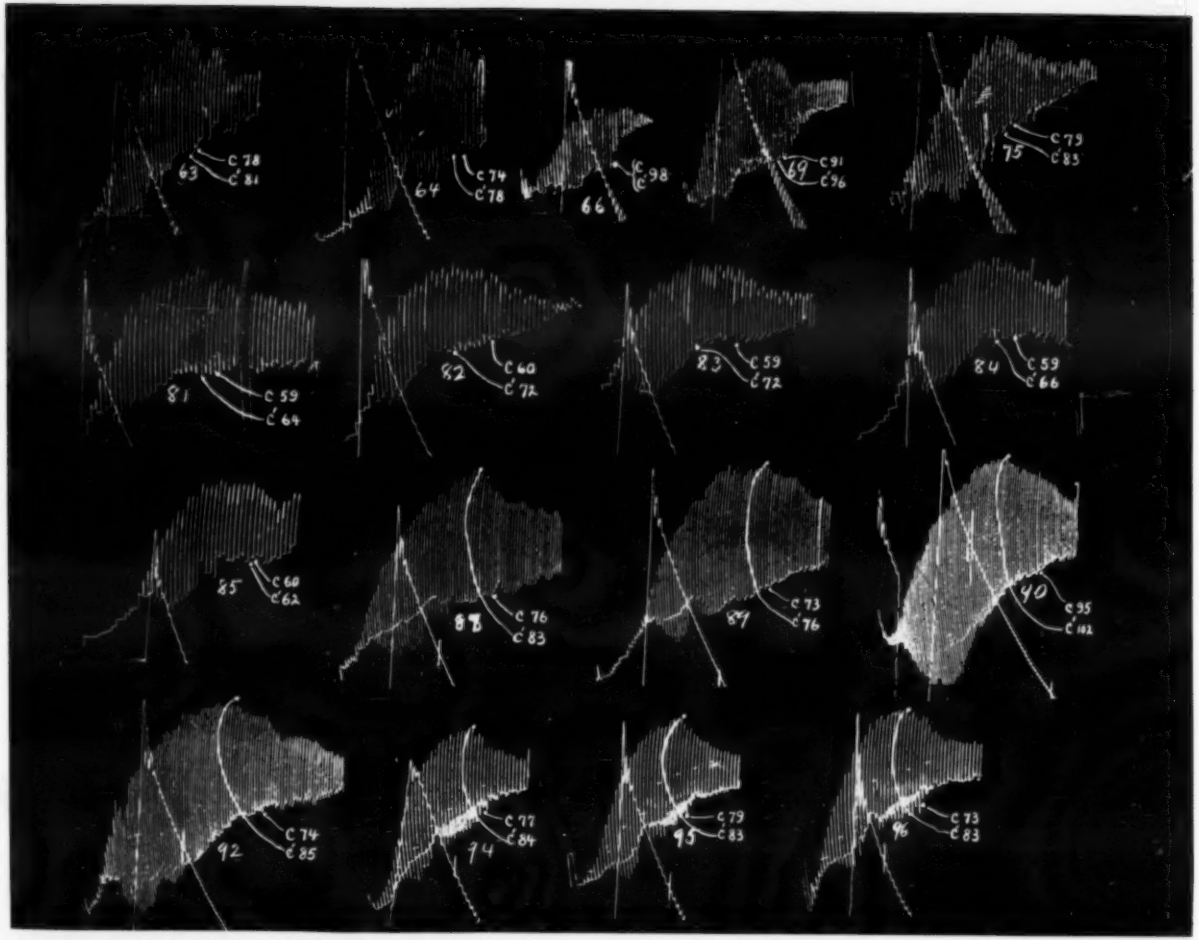

Fig. 8.—Oscillatory tracings marked at two different times by the same individual. C = marks made in 1912; C' = marks made in 1913. Diastolic readings; 21 per cent. reduction.

In glancing over the illustrations it will be noticed that there is comparatively little agreement with regard to which records are suitable and which are not. "C," for example, who criticizes or questions many tracings which all the others consider satisfactory, marks without hesitation a number of records which are not clear to them.

As a basis for comparing the readings by different men, only those records are taken which were marked by all six and were not classified as faulty or doubtful by any of them. If only one observer failed to mark a record (although in some cases this appears to have been due to oversight), or made two marks for systolic or diastolic reading, or expressed doubt about his mark, that record was thrown out. Or, strictly speaking, that part of the record ("systolic part" or "diastolic part") was thrown out. So that, in the tabulation which follows, it is to be understood that the only tracings referred to are those which met with unanimous approval;[1] and they are to be recognized in the illustrations by the absence of notations above them. There are thirty-six such tracings for comparison of systolic determinations and fifty-six for diastolic.

THE SYSTOLIC READINGS

In almost all cases there is a great dispersion of points chosen for systolic readings. In tracing No. 19, concerning which there is least disagreement, there is a difference of 8 mm. of mercury between the highest and lowest mark, while in No. 49 the difference is 62 mm. of mercury! Figure 9 shows the relation between the number of records and the amount of this scattering. It will be seen that a majority of the tracings show differences between highest and lowest marks of from 15 to 35 mm. of mercury. The average is 29 mm. or 22.2 per cent. of the average of all the systolic readings.

The surprizing magnitude of these discrepancies prompts an inquiry concerning the possible causes.

That many of them are due to the lack of uniformity of ideas with regard to the criteria is suggested by the fact that the readings of certain observers are usually higher than those of others. Thus, the average of "C's" thirty-six systolic readings is 110 mm. of mercury, while that of "F" is 132.5, of "B" 133.4, of "E" 134.5, of "D" 135.7, and of "A" 138.4. The statements of their criteria are the following:

"A": A sudden increase in the amplitude of the beats, especially when this involves a fall beneath the base line.

"B": I either used the moment of sudden increase in the height of the curve, or when this wasn't clear, a little jump in the curve which Erlanger has described as a criterion.

1. One general criticism referring to the speed of the drum will be referred to later.

"C": The sudden increase in amplitude of oscillations, and especially change in form of oscillations.

"D": The point at which the upper and lower margins of the oscillations diverge to form a —<. In doubtful cases this is often aided by the presence of a small shoulder to the right of the descending limb.

"E": Two guides, sometimes one, sometimes the presence of both, were used as indicators for the systolic blood pressure, that is, (a) the first decided increase in the excursions of the lever and (b) the presence of the small shoulder at the base of the line recording the fall of the lever.

"F": Did not state his criteria.

Thus it appears that "A," "B" and "D" look primarily for the sudden increase in amplitude, the two latter resorting to the change in form of the wave in doubtful cases; "E" uses either of these criteria without preference; while "C" looks especially for the change in form. The significance of these variations in the understanding of the criteria will be referred to later.

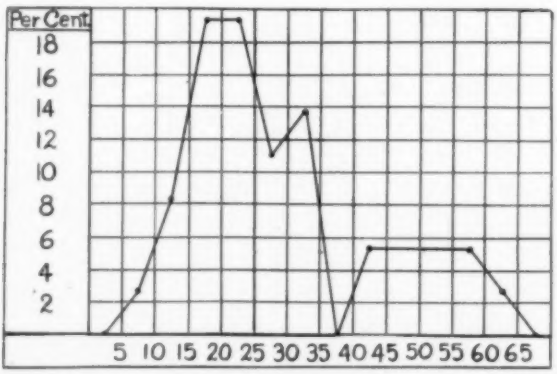

Fig. 9.—Relation between the number of tracings and the scatterings of the systolic marks. Numbers at left represent percentages of total number of tracings (36) accepted for the analysis; at bottom the differences between highest and lowest readings on a tracing expressed in millimeters of mercury.

THE DIASTOLIC READINGS

The scattering of points marked for diastolic readings is about as extensive as for the systolic readings. In Tracings 9 and 10, concerning which the disagreement is least, the difference between highest and lowest, expressed in millimeters of mercury, is 4 mm. The greatest difference is 46 mm. in No. 91. Figure 10 shows the relation between the number of records and the amount of scattering. Here the greatest number of tracings shows a scattering of between 10 and 25 mm. of mercury. The average is 18.5 mm. While, absolutely, this figure is less than the average scattering of systolic readings, it is relatively practically the same, that is, 21.3 per cent. of the average of all the diastolic readings.

Here again, certain observers usually make the low marks, and others the high ones. And again the discrepancies may be explained by differences in the ideas as to the exact criterion of diastolic pressure. The following quotations indicate the criteria of "A," "B," "C," "D," and "E":

"A": The criterion for the diastolic pressure was the last of the large beats, that is, the beginning of the definite diminution in size.

"B": The diastolic pressure was placed according to the rule that it coincides with the last oscillation of maximum extent.

"C": The first sudden and consistent diminution in amplitude of oscillations.

"D": The diastolic pressure was estimated by the last of the beats of maximal amplitude.

"E": I have chosen the first apparent maximum oscillation without making measurements of the tracings.

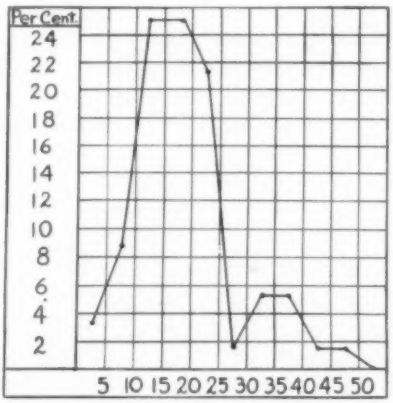

Fig. 10.—Relation between the number of tracings and the scatterings of the diastolic marks. Numbers at left represent percentages of the total number of tracings (56) accepted for the analysis; at bottom the differences between highest and lowest readings on a tracing expressed in millimeters of mercury.

The ideal tracing on which these five might agree would show oscillations steadily increasing to a maximum and then at once diminishing abruptly. But if this condition fails to occur, the opportunity for confusion arises. In tracings like Nos. 1, 3, 35 and 52, in which a number of the largest oscillations seem to have about the same amplitude "E" will mark the first of them, "B" and "D" the last of them. If, following these maximal oscillations, the reduction in size is not at once abrupt, as it very often can hardly be said to be, "A" will wait for a "definite" and "C" for a "sudden and consistent" diminution in amplitude.

"B" and "D" define their criterion in almost exactly the same words, and yet in only seventeen out of the fifty-six records do they

prick the same spot. Their differences vary up to 36 mm. of mercury (No. 90) and average 4.5 mm., even though their criterion would seem to be the easiest to follow. Of course, they used only the eye for measuring the length of strokes, but they had the advantage of leisure, of having the completed tracings before them, and of confining their attention to the oscillation record exclusively, which is not the case in the ordinary use of the Erlanger apparatus, using the method of continuous escapement.

"A" and "C" seem to express practically the same idea with regard to the diastolic criterion, namely, the first more or less abrupt contraction in the length of the strokes after passing the maximum. But intervals between their marks are more constantly found and have a higher average than in the case of "B" and "D." They have to gage not only the length of the strokes to determine the maximum, but also the rate of decrease in amplitude from point to point in the tracing, and they have to decide where this decrease becomes "definite," or "sudden and consistent." One does not have to look far to see the difficulties involved in these judgments, for example Nos. 23, 79, 82, 83.

THE PULSE PRESSURE

The pulse pressure, being the difference between systolic and diastolic pressures, shows in these tracings a combination of the vagaries from the two sources. Twenty-eight of the tracings escaped specific criticism for both systolic and diastolic determinations. Among these it is possible to compute from identical tracings pulse pressures all the way from 3 to 97 mm. of mercury (No. 48), from 0 to 73 (No. 53), etc. The average of the lowest computable pulse pressures in these twenty-eight records is 13 mm., of the highest, 58 mm. And in several of the records which were thrown out on account of a single criticism, relating to the speed of the drum, the lowest computable pulse pressures are minus quantities—in No. 90—27 mm. of mercury; that is, one observer's diastolic reading is actually 27 mm. higher than another's systolic reading. Of course, such results could not occur if the computations were limited to the marks of any one individual.

II

As has been stated, there was among those who marked the tracings some lack of uniformity of ideas as to exactly what phenomena constitute the oscillatory criteria both for systolic and for diastolic readings. It seemed very desirable, therefore, to determine how much variation may occur in the choice of reading points when the possible occurrence of this disturbing factor (difference of ideas with regard to the criteria) is removed. This would be shown by a comparison

of two sets of marks made at different times by the same individual on copies of the same tracings; the second marking to be done after a considerable time interval. Dr. Erlanger has very generously consented to be the subject of this experiment, and has marked systolic and diastolic points on a fresh set of photographic prints identical with the ones which he with the others had marked before. The first prints were marked in December, 1912, the second in November, 1913. Both times he responded to the request to indicate which tracings were to be considered unsatisfactory for reading, referring to the tracings by number and making remarks favorable or otherwise about most of them; in 1913 he did this without referring to the copy of his 1912 letter. Both times he made the general criticism that the slowness of the drum interferes with the recognition of the change in form of the down strokes. For systolic readings there were classified specifically as faulty or doubtful forty-four tracings in 1912 and ninety-two in 1913; for diastolic readings thirty-two in 1912 and sixty-one in 1913.[2] Some tracings, such as Nos. 9, 10, 32 and 33, which were given systolic marks without comment in 1912, are described in 1913 as "not legible." Nos. 94 and 95 each have two widely separated marks in 1913 and one mark without comment in 1912; No. 41 in 1912 was said to be doubtful for diastolic reading; in 1913 the diastolic mark is placed without question, both marks, however, very near together.

As a basis for comparing readings made at the two times only those tracings have been used which escaped specific criticism both years. Of these there are six for systolic readings (Nos. 3, 12, 20, 21, 23 and 26, the top row in Figure 7) and thirty-two for diastolic readings (the remainder of Figure 7 and Figure 8). On these plates C indicates the first marking and C′ indicates marks placed eleven months later. The values in millimeters of mercury are given; they have been determined as described in Part I.

SYSTOLIC READINGS

In each of Records 3 and 12, two points for systolic reading were marked in 1912. These have been included because it was specifically stated in 1913 that No. 3 "seems satisfactory"; although in other instances the marking of two points on a tracing for systolic or diastolic reading has been considered reason for excluding that tracing. In No. 3 the 1913 mark is the same as one of the 1912 marks, and in No. 12 it is within 5 mm. of mercury of one of the 1912 marks. In the remaining four systolic comparisons the differences between the 1912

2. Whenever the criticism of a tracing was not clearly stated to refer either to the systolic or diastolic part of the record it was assumed to refer to both parts.

and 1913 marks are respectively: 22, 8, 16 and 18 mm. of mercury; an average difference of 16 mm. or 13 per cent. of the average of these eight readings. Among other tracings which escaped specific criticism either in 1912 or 1913, but not both times, there are still larger discrepancies between the two systolic marks, which run as high as 30 mm. of mercury in Tracing 8.

DIASTOLIC READINGS

Among the thirty-two diastolic comparisons the differences range from 0 to 16 mm. of mercury, and average 5.4 or 6.9 per cent. of the average of these readings. Among some of the other tracings which escaped specific criticism in one of the years there are differences in diastolic readings up to 23 mm. of mercury in Tracing 47.

DISCUSSION

The principal object which has led to the use of the oscillatory criteria instead of simple palpation or auscultation of the artery below the cuff is the avoidance of errors involved in the identification of the criteria—tactile sensation and even hearing being supposedly less sensitive for this purpose than vision. Only an occasional statement in the literature of the subject is at all skeptical,[3] and the feeling is general that the clinical use of the simpler methods of palpation and auscultation is dictated by economy and convenience at the expense of a certain amount of accuracy. Of course, this preference should not be given to vision without a consideration of what the observer is expected to see, and it is remarkable that the oscillatory criteria have received such general acceptance on this basis without any attempt being made heretofore to determine the personal factor involved in their identification and to compare it with similar sources of error in the use of other methods. Tests comparable as closely as possible to those here reported have now been applied to the palpatory[4] and auscultatory[5] indices; and the analysis of the results is decidedly favorable to the simpler methods.

This investigation has nothing to do with the general question of sources of error in blood pressure measurements, which has been reviewed elsewhere.[5] It has no bearing even on the truthfulness of the oscillatory indices, once they are accurately identified; and it is in no wise to be regarded as an attack on the important experimental work of Erlanger and others in support of the validity of particular oscillatory criteria. It is concerned solely with the quantitative deter-

3. Cordier and Rebattu: Arch. d. mal. du coeur, 1911, iv, 737.
4. Kilgore, E. S.: California State Med. Jour., March, 1914.
5. Kilgore, E. S.: Page 927, this issue.

mination of the personal factor which operates in the clinical interpretation of these criteria, and it shows that this factor may be surprisingly great. The six men who made the experiment possible by submitting their marks fortunately are physiologists and clinicians whose qualifications cannot be questioned.

The first important fact to appear is that there is little agreement with regard to the fitness of individual oscillatory records, which to accept for reading and which to throw out. The records were not selected in order to show difficulties but were taken at random from among hundreds of others; and with the exception of one statement with regard to the speed of the drum, which will be referred to later, no one has made any general criticism of them.

The second exhibit is the variety of understandings as to the exact criteria both for systolic and for diastolic pressure. This alone is sufficient to invalidate all reports of blood pressures obtained by the oscillatory method which do not state very precisely the criteria employed. The claims of these various criteria cannot be discussed here; but, in view of the extensive use of this method in the past, not only in practical clinical work but also by investigators as a "control" or means of standardizing other methods, it is important to emphasize the fact that *there is not a general and exactly uniform understanding of the criteria.*[6]

It is evident from a comparison of the systolic marks made by different observers and their statements of the systolic criteria that some of the confusion here arises from the attempt by different men to follow two different criteria, which often appear not to coincide.

The sudden increase in amplitude ("principle of von Recklinghausen") is the criterion generally accepted among those who employ the oscillatory method with whatever instrument used. Erlanger,[7] after extensive experiments, adopted it for use with his graphic method, and later[8] described the "change in form" of oscillation record (a shoulder on the down stroke) as an additional systolic criterion. Both have been given adequate theoretic and experimental support, and they should of course and in selected instances do

6. Nearly always among the diastolic marks "E" is highest and "C" lowest. The differences between these two are responsible for a considerable part of the total average discrepancy, and the omission of either "C's" or "E's" marks reduces the average by 5 mm. of mercury. It is not the purpose of this paper to offer criticisms or suggestions about the marks, but it is fair to point out that in all probability a considerable part of the diastolic differences of "C" and "E" could have been avoided by a previous conference between them. Their statements of the criterion, it will be recalled, were not the same.

7. Erlanger, Joseph: Rep. Johns Hopkins Hosp., 1904, xii, 53.

8. Erlanger, Joseph: Am. Jour. Physiol., 1908, xxi, 24.

obviously occur at the same points in the tracings, but it is also a fact that in practical application on human beings they frequently lack at least the *appearance* of doing so.

When these tracings were made it was not considered desirable to make a special comparison between the two systolic criteria, and a rather slowly moving drum was used, thus bringing the strokes moderately near together and accentuating changes in amplitude, on which depend one of the systolic criteria and the only available diastolic criteria. This compacting of the records has rendered the change in form less conspicuous and in some instances has obscured it entirely. One general criticism (to be referred to again) has been made on this account; hence, even though the change in form is distinct in many of these curves they are not to be urged as examples of the apparent failure of the two criteria to coincide. But reproductions of oscillatory curves appearing in the literature show the same characteristic—for example, a tracing published recently by Erlanger and Festerling.[9] By actual measurements the approximate lengths in millimeters of successive up-strokes (here designated consecutively by letters) from the beginning of the first oscillations are: (a) 0.3, (b) 0.6, (c) 0.4, (d) 0.4, (e) 0.5, (f) 1, (g) 2, (h) 2.4, (i) 4.4, (j) 6.3, (k) 6, (l) 7.8, (m) 7, (n) 6, (o) 7.9, (p) 7.3, (q) 6.9.

The change in form begins definitely with Stroke m. At this point the increase in amplitude, as the measurements show, is a minus one as compared with the abrupt positive increases in the region of Strokes e to i. The greatest single absolute increment is between Strokes i and j, the greatest relative increments betwen Strokes e and f and between f and g.

Certainly both of these criteria should not continue to be relied on unless at least an understanding of them can be reached which will prevent their ever appearing to conflict; and in these experiments it may be presumed that if the observers had all confined themselves to one criterion and marked only the records in which this was clear, the differences in systolic readings might have been less. But—

Third: The very great discrepancies disclosed between the readings of different observers are only partly explainable by variations in the understanding of the criteria. Those who endeavor to follow what appear to be identical criteria frequently choose widely separated reading points both for systolic and for diastolic readings.

Fourth: After completely eliminating the possibility of variations in the understanding of the criteria influencing the results, there still remain large disagreements in the choice of reading points. The one who may be presumed to be best qualified in this country to identify the

9. Erlanger and Festerling: Jour. Exper. Med., 1912, xv, 370, Figure 4b.

oscillatory criteria, seldom on second trial duplicates his first marks, and often misses them by a wide margin. His average discrepancy for thirty-two diastolic comparisons is 5.4 mm. of mercury or 6.9 per cent. of the average of all these diastolic readings; the average discrepancy for the four systolic comparisons is 16 mm. of mercury or 13 per cent. of the average of these systolic readings. In connection with this systolic result must be taken into consideration the general criticism mentioned above, and to be referred to again, relating to the slowness of the drum.

Fifth: In weighing the results of these experiments as a whole it must be remembered that several sources of error have here been excluded which are present in actual practice with the Erlanger apparatus. In using the ordinary method of continuous escapement it is necessary to divide the attention between the smoked record and the mercury column, to decide about the criteria the instant they are supposed to occur without having the completed tracing for comparison, and to read the level of the mercury column at once, the latter itself being in active up and down movements. In this experiment the observers have had the benefit of unlimited time for consideration, of reading records already completed, and of giving them exclusive attention. The conclusion is inevitable that in actual practice by these observers, if they worked independently and *relied exclusively upon the oscillatory criteria,* using the ordinary method of continuous escapement, their blood pressure measurements would be even more discordant than is shown here.

Sixth: Whatever this experiment shows with regard to the personal factor in the results obtained by the Erlanger instrument would seem to apply with even greater force to the use of all the other blood pressure instruments hitherto described, with which the oscillatory criteria exclusively are used; for with the possible exception of a photo-registration method, Erlanger's instrument appears to be unquestionably the most perfect on the market for the purpose for which it is designed, namely, to show graphically the pressure oscillations in the pneumatic cuff used for compression. Uskov's apparatus[10] has no features to save it from the discordant readings exhibited in this experiment; but on the contrary, it has been clearly shown[11] to have unequal sensitivity at different pressures—a condition calculated to distort markedly the oscillatory criteria. Another well-known graphic instrument is that of Gibson,[12] which registers the oscillations of the

10. Uskoff: Ztschr. f. klin. Med., 1908, lxvi, 90.
11. Erlanger, Joseph: A Criticism of the Uskoff Sphygmotonograph, THE ARCHIVES INT. MED., 1912, ix, 22.
12. Gibson: Quart. Jour. Med., 1907-1908, i, 103.

mercury column itself. The change in form of the wave does not appear at all in these tracings, and the changes in amplitude are gradual. Simultaneous records made by an Erlanger oscillation recorder and a float in a mercury manometer, both connected with the same cuff, show very gradual alterations in amplitude of the swings of the mercury column even when the amplitude changes in the other record are quite pronounced. Mercury is far too heavy to respond promptly to these changes in oscillation amplitude.

Many blood pressure instruments are supplied with a pointer on a dial, a pith ball or drop of fluid in a glass tube or other device for exhibiting pressure oscillations in the compressing cuff without making a graphic record. The observer is expected to carry in his mind the amplitude of preceding oscillations and accordingly to form his judgments of the amplitude changes. It is evident that in this attempt he is still further handicapped by not having before him a graphic record of the oscillations preceding the place where he makes his reading.

Professor Erlanger, who does not entirely agree with the inferences which it seems to me must be drawn from these experiments, is kindly stating his views in an accompanying paper. The points in his article which it would seem advisable to mention in this separate connection are the following:

1. The Conditions Affecting these Experiments: In so far as the recognition of the "change in form" is concerned, Professor Erlanger is justified, I believe, in his two general criticisms relating to the adjustment of the apparatus; namely, that the smoked surface traveled more slowly and that the writing lever magnification was greater than optimum; or rather that the relation between these two adjustments was not the best for showing the "change in form." So that, although the "change in form" is quite clear in many of the tracings, and although all tracings were omitted which seemed doubtful to any of the observers, yet it is fair to reserve judgment of the personal factor involved in the use of that criterion. In common with the majority who, up to the present time, have attempted to use the oscillatory criteria with whatever instrument, I was looking especially for the sudden increase in amplitude as systolic index. As has already been explained, this as well as the diastolic criteria, is rendered more distinct by the slower drum, and the same is true of the greater lever magnification.

That Professor Erlanger has now abandoned "the first sudden increase in amplitude" as an index of systolic pressure in the method of continuous escapement is an important announcement, which especially deserves consideration by those who are still advocating the use

of the oscillatory criteria with nongraphic instruments. So far as I am aware, no one claims, without the employment of graphic oscillatory records, to be able to use either the "change in form" as a criterion or the oscillatory indices by the method of intermittent escapement.[7] Additional sources of error in interpreting oscillatory indices with nongraphic instruments have already been pointed out.

With regard to all the oscillatory criteria except the "change in form," I do feel that, for the purposes of this investigation, the conditions under which the curves were obtained and interpreted were excellent. While the presence of the graphic manometer record obviated the necessity of immediately reading the mercury level, efforts were not lacking constantly to adjust the apparatus to get the best curves; and the resulting mixture of good and bad tracings is what always occurs in practice. The personal factor immediately becomes evident in selecting the tracings which should be read, and one of the important showings of these experiments is the magnitude of the personal factor which enters into this choice. No practice of "redetermining the end-points" in doubtful curves could obviate the necessity of first deciding which were the doubtful tracings. Most of those who marked the records gave free expression to doubts or criticisms connected with individual tracings; and, while these criticisms did not agree, all the tracings were thrown out of further consideration which received an expression of doubt from any one of the six men—a weeding-out process considerably more radical than would be the case if one of these men were using the method in practice. It certainly does not seem too much to assume that the tracings which remain after this more than ordinary discrimination represent at the most the ones which the average person using the method would attempt to read without further checking up the "end-points" by other methods. And if these selected tracings are not to be relied on without verification from outside sources, it is difficult to see what circumstances would ever enable them independently to be given full confidence.

2. The Factor of Interest or Concern: It is true that these six observers were busy men. They were at liberty to decline to spend time with this matter; but, having once consented to be subjects of a scientific experiment, it is entirely fair to assume that they did not slight it, but that, on the contrary, if there was any difference between their psychologic attitude to this task and to the ordinary one of routine blood pressure determinations, their more careful efforts were bestowed here. And, however gloomy may be the outlook for quantitative clinical methods in view of "E's" failure to mark the maximum oscillations, it is impossible to derive reassurance from the assumption that he would have done better if his judgments had been

formed in haste on uncompleted records and with his attention divided between them and the mercury column.

3. The Factor of Judgment: The quantitative determination of the effect of this factor, it must be remembered, has been the chief object of this investigation. Professor Erlanger believes that the absence of a series of determinations obtained from each subject "at the same sitting and under as nearly the same conditions as possible" has deprived the observers of a "legitimate aid to the formation of a judgment." My answer is that the usual shifting character of blood pressure due to respiration or other causes makes series of determinations always preferable to single ones in actual blood pressure measurements with any method; but that within the scope of this investigation, which is sharply limited and which does not include actual blood pressure measurements, such series would be out of place. To illustrate, if the problem put to these observers had been to determine the blood pressure of a given subject, it would have been advisable for them to rely on a series of readings from this subject; and they would have been confronted with the double task of first making the individual readings in the series, and, second, if there was variation in the results, deciding what values to accept. In this experiment, on the contrary, they have had but the one problem of selecting the reading points in the individual tracings; and all that was necessary in order for them to obtain 100 per cent. accuracy within the limits of this investigation was to throw out the ambiguous records and choose identical reading points in the remainder, even though the corresponding reading of the manometer was far from the true blood pressure. The requirement of a series of graphic records, in order to discredit individual tracings which by themselves apparently are legible, is certainly a testimony to the uncertainty of the criteria afforded by those tracings.

Moreover, in order to utilize a series of records from the same subject to check up individual readings in the series, it is necessary as Professor Erlanger suggests, to assume that all were taken under practically the same conditions, that is, at practically the same blood pressure. Yet in another place he refers to the well-known fact that the blood pressure cannot be depended on for stability, but frequently undergoes considerable variations over periods of a few moments. To the credit of the palpatory and auscultatory indices it should be remembered that readings by these methods suffer no indefiniteness on account of changes in blood pressure.

4. The Comparison of the Diastolic Marks Made by One Observer: In connection with the average discrepancy of 5.4 mm. of mercury or 6.9 per cent., the following facts must be taken into consideration:

(*a*) This 6.9 per cent. is not a measure of the total error involved in the method, but only of that due to one factor, namely, the judgment latitude of a single observer in selecting the reading points. It must be presumed that this latitude would be increased if the judgments of more persons were involved, however uniform their training in regard to the criteria to be looked for. In practice, also, the personal factor plays a further rôle in reading the manometer, and as in other methods, additional sources of error, such as resistance by artery walls or arm tissues, may assert themselves. Furthermore, if my contention is correct that single tracings rather than a series from the same subject offer the proper basis for determining the play of judgment in identifying the criteria, then the chances for minimizing the personal factor in this effort were considerably better in this experiment than in actual practice, because of the opportunities here enjoyed of marking completed tracings without the need for hurry in making the decisions or for diverting the attention from the tracings to the manometer.

(*b*) Notwithstanding the elimination of doubtful tracings both times they were marked, discrepancies as high as 16 mm. of mercury occur; and among records which were accepted one year but not both years discrepancies as high as 23 mm. of mercury are found.

(*c*) Parallel experiments with the auscultatory diastolic criteria[5] although necessarily containing additional sources of error, connected with the reading of the manometer and the inclusion of the readings of two observers instead of one, have shown discrepancies averaging only one-third to one-half as much as in this test.

The limitation of the scope of this investigation must again be emphasized. No evidence is presented either for or against the correctness of the oscillatory indices *once they are acurately identified*. The fact that individuals who express the criteria in almost the same words may really understand them quite differently is important, and will give special interest to the rediscussion of the identifying features of the curves in Professor Erlanger's article. These experiments should by no means be counted to the discredit of graphic methods in general; but they will do good if they are accepted as strongly emphasizing the need for more careful discrimination in the use of instrumental clinical procedures which lay claim to special accuracy.

I am very grateful to Drs. Cabot, Cannon, Erlanger, Hewlett, Henderson, Hirschfelder, Janeway, Moffitt, and Wilbur for their cooperation. It will of course be understood that those who submitted themselves as subjects of these experiments are in no way thereby committed to the method. Drs. Cabot, Henderson, and Janeway, who did not mark the tracings, permit the publication of the following extracts from their letters which show why they did not:

R. C. CABOT: I must confess myself totally unable to mark any point to be regarded as the diastolic pressure in the tracings which you sent me. . . . I am very glad you are bringing out the unreadability of Erlanger's records.

YANDELL HENDERSON: After looking over your records, it is quite clear that in the majority there is *no one* maximal pulsation that would mark diastolic pressure. They confirm my previous opinion that even the Erlanger instrument usually gives a very indistinct criterion of diastolic pressure. The point of sudden increase at systolic pressure is clearer, although often also obscure. My answer is then that there are *no sharp* points of transition, and it would be useless to mark what is *not there*. It would be mere guess work.

THEODORE C. JANEWAY: I found long ago that in many cases it was quite impossible to determine the lowest point of maximal oscillation on an Erlanger record, or in any other way. In some pulses the point is fairly clear cut, but I believe they are in the minority. Since the introduction of the auscultatory method, I have lost my interest in the oscillatory and have given the matter no thought. So far as estimation of the systolic pressure is concerned, I do not believe in attempting this by any device which registers changes in the portion of artery being compressed, and I have at no time used the Erlanger systolic index. Auscultation checked by palpation immediately below the cuff makes, I think, the best method for systolic readings.

AN ANALYSIS OF DR. KILGORE'S PAPER: "THE LARGE PERSONAL FACTOR IN BLOOD PRESSURE DETERMINATIONS BY THE OSCILLATORY METHOD" *

JOSEPH ERLANGER, M.D.
ST. LOUIS

In a spirit that cannot be too highly commended, Dr. E. S. Kilgore has submitted to me the first draft of his manuscript together with a letter stating that "it would be decidedly to the advantage of the truth-seeking medical public if, after reading my manuscript, you would present your criticism in the form of an article to appear in the same journal number. . . . If you will do this I should like to have the privilege of reading your manuscript and, if indicated, altering my own, and we would then exchange manuscripts again until there were no further changes to make."

Convinced by my experience as well as that of others, with the graphic oscillatory method of determining the blood pressure; by the satisfactory check to which it has been subjected by the experiments on animals, performed by myself and others, and by observations made both by myself and others, in which, at the same time, the blood pressures have been determined by the palpatory, oscillatory, auscultatory and subjective methods, that the oscillatory criteria, when properly checked, are not alone as sharp but are also as accurate in the determination of the blood pressures as any other known method[1] while possessing the additional advantage of objectiveness, I feel that lest the effect of Dr. Kilgore's critical studies may be to

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* From the Physiological Laboratory of Washington University, St. Louis.

* Since this was written I have had the opportunity of reading Dr. Kilgore's manuscript on "A Quantitative Determination of the Personal Factor in Blood Pressure Determinations by the Auscultatory Method," in which he presents the results of an investigation of the errors in judgment involved in reading the blood pressures by the auscultatory criteria. He finds the error in judgment to be less than in the case of the oscillatory criteria. In reply to the results therein recorded I wish to say now that in observations made by my students under conditions as objective as it is possible to make them, the agreement between the systolic readings as made by the "change in form" criterion and the auscultatory criterion is exact to the pulse wave, while for the diastolic pressure it is exact to within two or three pulse waves.

1. As a matter of fact, the auscultatory method was not generally accepted until it was shown that its readings agreed in general with those of the oscillatory method, while the auscultatory phenomena have received their explanation through experiments in which readings of the oscillatory and auscultatory methods have been compared.

curtail the use of this method, or to cast doubt on recorded results obtained by it, it is my duty to avail myself of the opportunity so considerately afforded of replying to Dr. Kilgore's criticisms. At first I had hoped to do this in a constructive way, by gathering for my reply new data with special reference to the points raised by Dr. Kilgore. Unfortunately, however, the press of other work has rendered the preparation of such a reply impossible at this time. I hope, though, that I may soon have the opportunity of presenting such data. In the meanwhile I must content myself with a criticism of Dr. Kilgore's methods based on logic and on past experience with blood pressure methods.

II

In the first place let me say that while Dr. Kilgore's results demonstrate beyond peradventure that the determinations of the blood pressure by the *continuous escapement* modification of the oscillatory method, when not checked by well-known procedures, obviously may give rise to much confusion and uncertainty, it should nevertheless be borne clearly in mind that the method of intermittent escapement, a more definite, though slower, procedure than the method of continuous escapement and the one that was used when this subject was in the experimental stage, is not here the subject of discussion. The object of this reply is to point out the pitfalls that may be encountered in the use of the method of continuous escapement and the way to minimize them. At the same time it will be necessary to indicate some places where, in our opinion, Dr. Kilgore might with advantage have employed slightly different methods in approaching his problem.

Dr. Kilgore maintains that by his method of procedure the discussion of his results is limited to certain topics only; that these do not include "the general question of sources of error in blood pressure measurements," or the "truthfulness of the oscillatory indices, once they are accurately identified."

I am perfectly willing to submit to this limitation of the discussion if Dr. Kilgore, on his side, is ready to maintain that his records were made and controlled under the best of conditions, or even under conditions that ordinarily should obtain in routine observations. The fact that he included in his critique only such records as were read without question by those to whom they were submitted, does not, for reasons to be given below, materially modify our consideration of this point.

Let us then examine Dr. Kilgore's methods. With the Erlanger sphygmomanometer he made a large number of tracings, over 1,300, recording simultaneously with the oscillations by means of a mercury

manometer the pressure in the cuff as it was gradually falling.[2] We are led to suppose that no earnest endeavor was made to interpret these records until all had been made. In other words Dr. Kilgore must have assumed that the process of reading a blood pressure record is similar to the process of reading ideal instruments of precision, for instance, the scale of a galvanometer which is being deflected by a steady current. In doing this he has failed to realize two important considerations: (1) he has failed to realize that the blood pressure criteria, like the end-points of volumetric chemical determinations, can be altered with respect to distinctness through changing conditions, and (2) he has failed to realize the significance of the personal factor as affected by his particular methods.

(1) Blood pressure criteria are not equally clear under all circumstances. When they are not clear it is usually possible, by means of slight changes in the adjustment of the apparatus, for example by changing the magnification of the oscillations by simply shifting the tambour in or out, to bring them out with unmistakable clearness. Furthermore, the form of the record may be materially altered by the variable conditions under which they must be made. If proof of variability in form is desired, it is only necessary to inspect the records published by Dr. Kilgore. Among them can be found at least a dozen different types. With the change in type, the criterion one is accustomed to look for may be difficult to recognize. Now if one finds on reading a record that he is in doubt as to the points he should select as indicative of the pressures he is seeking to determine, the attempt should then and there be made to redetermine the "end-points" by making a record by the method of intermittent escapement. I can assert that in the vast majority of instances the difficulty can by this procedure be made to disappear. If not the method of intermittent escapement alone should then be used.

Dr. Kilgore's failure to appreciate these facts has presumably gotten him into his dilemma. Without ever stopping to determine whether his end-points were clear, and, if not, whether they could be made so, he has proceeded to make long series of records. He then finds, when the time arrives to read his records, that many of them seem to be illegible. On consulting others he finds that while some essay to read

2. I am inclined to believe that the larger mercury manometer that must be used if the fall of pressure is to be recorded by a float, on account of its greater oscillation and greater mass, will have a tendency to eliminate the characteristic criteria of the oscillatory record.

most of the records without question (of this more later), others hesitate to read any.[3]

I do not by this discussion mean to give the impression that it is possible in every case to obtain clearly the criteria for reading the pressures. Rarely, however, when at first there is difficulty in finding the marks, is it impossible to obtain, by slight readjustment of the apparatus, criteria that give perfectly clear and consistent readings.

We may therefore conclude that while Dr. Kilgore's records may represent the kind that one is often called on to read in practice, there are reasons for believing that if he had used the procedure which it is advisable to employ in practice, he would have secured clearer records and consequently more consistent readings.

(2) These records were then submitted to a number of observers with the request that they mark the "satisfactory ones." By discarding those not marked, as well as those marked but questioned, Dr. Kilgore believes that he has removed from consideration all records which, through faulty technic or accident, are not up to standard, or conversely that the records marked were entirely satisfactory and as good as those ordinarily made. We have already given reasons which indicate that Dr. Kilgore did not obtain as clear records as it is possible to get. The fact, however, remains that these records were marked and that there was no agreement among the different observers as to which records were satisfactory and which unsatisfactory.

In connection with these facts it is necessary to examine into the psychology of a problem of this kind.

(*a*) Is it not legitimate to ask in this connection: "Would the same persons have accepted without question similar records made in the course of their own work? Is it not possible that the critical attitude, with which one is in the habit of interpreting results he is in a position to control for himself, might have been warped by the request to "mark the records?"

(*b*) Furthermore, when readings are made, on the one hand, by one whose whole soul is in the investigation, and, on the other, by one who is asked to make the readings as a favor, and who, therefore, takes only a casual interest in the affair, there can be no question as to which of the two sets of readings will be the more dependable. When, in addition, one who is not directly interested has the task set him of carefully selecting two points on each of 100 records, a matter which,

3. For example see Henderson's letter. I agree in large part with Henderson's criticism, for I, too, found it impossible to read many of the tracings with any degree of certainty (Consult Dr. Kilgore's paper). The results of my two attempts to indicate the diastolic pressure, showing an average difference of only 5.4 mm. of mercury, prove that the diastolic pressure index, even in these blindly made records, is not so indistinct as Henderson thinks it is.

if properly done, will consume a not inconsiderable part of a working day, it is obvious that the personal factor must become unusually large. An excellent example of the significance of this factor is to be found in the data submitted by Dr. Kilgore. "E" says, "I have . . . chosen the first apparent maximum oscillation without making measurements of the tracings."[4] Yet it is perfectly obvious on mere inspection of "E's" marks that he has not selected the highest oscillations. So impressed am I by his inconsistencies that I cannot refrain from directing attention to at least a few of them.

No. of Record	Amplitude of Oscillations	
	Marked by "E" mm.	Maximum * mm.
5	18	20
6	17	19.5
12	29	32
16	24	27
58	16	19
63	20	25
65	20	24
78	22	24
88	24	27
91	28	33

* I have not the information needed to determine in millimeters of mercury the differences between "E's" oscillations and the maximum oscillations. It is obvious, however, that it is not inconsiderable.

I do not, by this exhibit, mean to imply that "E" (whose identity is unknown to me) is an incompetent observer. I present it merely for the purpose of showing that disinterested opinion may often be of questionable value. There is no possibility of controlling in the same way the readings of the other observers, since the criteria they use are not definite enough for this purpose. If this could have been done I am inclined to believe that similar inaccuracies would have become evident. It might be maintained that this is purely and simply the personal factor that enters into all observations rather than the error resulting from disinterestedness. However this may be, if it could be convincingly maintained that "E's" readings represent the error involved in picking out the highest oscillations on a record and under the very best of conditions, I must confess that my faith in the data of "observers" would be rudely shaken, and I would then be inclined to suggest that we give up in despair our efforts to develop quantitative methods in medicine in general and in sphygmomanometry in particular. If relative amplitudes of recorded deflections cannot be judged, what confidence can we have in judgments based on a change in intensity of a sound or of an impact on the finger?

4. This, by the way, is not the accepted criterion of the diastolic pressure.

(*c*) The factor of judgment may next be considered. We have already referred to the fact that the sphygmomanometer record cannot be read in the same way as can a deflection on the scale of a galvanometer. The continuous escapement record does not present a steady crescendo to and then beyond the systolic mark nor a steady diminuendo beyond the diastolic mark. Rather we have superimposed on these a series of wave-like variations in amplitude, some regular, and due to the respirations, and some irregular.[5] So difficult it is on this account to locate the first sudden increase in amplitude that I have altogether discarded the use of that criterion in connection with the method of *continuous escapement,* and now judge the position of the systolic pressure by the "change in form" alone.

Be this as it may, it is obvious that when the criterion is the sudden increase in amplitude a double judgment is necessary. Such error as has resulted from this double judgment could have been minimized only by having placed at the disposal of the observers several records obtained from the same individual at the same sitting and under as nearly as possible the same conditions. In such records the systolic and diastolic changes in amplitude would have fallen in different phases of the respiratory waves and could then the more readily have been dissociated from them. A part of the variation in the readings of the several observers undoubtedly is due to their not having had at their disposal this legitimate aid to the formation of a judgment.

Nevertheless, it is obvious that many of the discrepancies in the readings of the different observers are too wide to receive their explanation in this way alone. As Dr. Kilgore points out in this connection, the trouble in part lies in not knowing the end-point to be looked for.

(*d*) Dr. Kilgore's study has also brought out some anomalous "judgments" which we hesitate to refer to because of the standing of the observers whose marks form the basis of the criticism. Since, however, Dr. Kilgore lays so much stress on the absence of agreement as to which records are satisfactory, I cannot refrain from asking just one question that may help to throw some light on the difficulty. I would like to know how "F" would justify his diastolic mark in Record 13? This he places without question in the midst of an irregularity obviously due to motion of the arm. While this is the most flagrant instance of this kind still there are many others to which the same criticism applies. It should be added, however, that if "F" had had

5. These waves are more marked in Dr. Kilgore's records than in those made in this laboratory. It would consequently seem that he did not observe as carefully as is possible the usual precautions to avoid the motions of the arm on the chest that occur in association with respiratory movements.

the opportunity of observing this record while it was in the making he would probably have recognized the cause of its fault.

Is it not possible, in view of the fact that a certain amount of judgment must be employed, that one investigator may regard as unsatisfactory a record acceptable to another; that the former may recognize, say, a disturbing respiratory wave which the latter fails altogether to take into consideration? Obviously, therefore, if each observer had had at his command a second record, or better, a series of records from the same subject made at one sitting and the opportunity of discarding inconsistent readings, there would have been a closer agreement on the question of readability of the tracings.

III

When I first saw Dr. Kilgore's records I stated that it was practically impossible in most instances to make use of the criterion of the systolic pressure, which I have designated the "change in form," because his drum had not moved fast enough. This criterion, it might be added, is by far the clearest and sharpest of the systolic criteria, in fact it is practically the only one that I now use. The speed that is necessary to bring this criterion out clearly is a relative matter, though in general it may be said that the criterion increases in clearness directly as the speed of the drum, which in Dr. Kilgore's experiments was not fast enough, and inversely as the magnification by the lever, which in most of Dr. Kilgore's tracings was greater than was necessary.

IV

Dr. Kilgore is quite right in insisting that if two criteria are actually indicative of the same thing, they must occur with the same pulse wave. Increase in amplitude[6] and the change in form should and do coincide in the vast majority of cases when they are clear. My experience convinces me that they fail to affect the same wave only through accident to the recording mechanism. It can, though very rarely, happen that as a result of vibration or draughts or roughness of the paper or what-not the lever does not press on the drum evenly throughout its entire excursion. It may happen that during the very wave that marks the systolic pressure the lever meets, say with increased friction, so that, while the change in form becomes manifest, the amplitude of the oscillation is not increased. As a matter of fact, the very record that Dr. Kilgore uses for the purpose of illustrating the lack of correspondence of the criteria gives clear evidence of the operation of some one such factor as the disturbing element; the lever here fails to sink to the general level of the record.

6. The increase in amplitude often is not clear.

V

With regard to the "puzzle" of submitting two sets of the same records to the same person for his opinion as to the location of the systolic and diastolic criteria, the results obtained, in view of what goes before, are "more interesting than conclusive."[7] The result was, however, very much as I had anticipated: rather wide discrepancies in the case of the systolic pressure, and fairly close average agreement in the case of the diastolic pressure. The discrepancy in the case of the systolic readings I expected would be large because the tracings "were not made on a surface that was moving with sufficient speed to bring out satisfactorily the change in form." The average error of 5.4 mm. of mercury in the case of the diastolic readings is no larger than the error inherent in the method itself; it is, therefore, well within the requirements of the method. The insignificance of this error can be made clear when it is pointed out that if in one reading the prick had been made just one pulse wave above a given pulse wave, and in a second reading just one pulse wave below the same wave, the error would, in many instances at least, have been practically 5 mm. of mercury. Greater accuracy than this is not to be expected in the present state of our knowledge. And when it is recalled that this good average was made in spite of certain wide discrepancies, amounting to as much as 17 mm. of mercury, obviously due to the disturbing influence of the respiratory waves, discrepancies which I am certain would not have occurred if we had had at hand the means we always have in practical sphygmomanometry of using only the consistent readings, one, I think, must be struck by the surprising agreement of the two sets of readings, rather than by the few instances of disagreement.

VI

In reply to Dr. Cabot's casual remark in regard to the unreadability of the diastolic pressure as indicated by the oscillatory method (for it is this rather than the reading by any specific instrument that he, undoubtedly, has reference to), I desire to make these remarks. (1) Even under the unfavorable conditions of Dr. Kilgore's test I succeeded in finding in both of two attempts thirty-two records that I thought were legible as regards diastolic pressure, and these I succeeded in reading with an average difference of 5.4 mm. of mercury. Evidently even under these circumstances, the records are not entirely unreadable. (2) Would Dr. Cabot care to maintain that the many investigators who, in comparative tests, have found the oscillatory

7. Quotation from my letter to Dr. Kilgore at the time the second set of records was marked.

criteria of the diastolic (and the systolic) pressure to agree, as well as could be expected, with the auscultatory criteria, could not or did not read their records? A more conservative statement, and one with which every one could agree, would have been that they are often unreadable. As I have previously said this could not be otherwise, because the blood pressure is not an immobile affair from which clear and identical records can be obtained time over and again. Rather, as a result of the play of the various blood pressure waves that is constantly going on during the period required in all methods for the determination of blood pressure, it is obvious that many of the readings by the method of *continuous escapement,* though by no means all, must inevitably be illegible. (3) Furthermore, I would like to know whether Dr. Cabot means to include in his sweeping condemnation, the readings made by means of the method of *intermittent escapement.*

Dr. Janeway's "opinion" with regard to methods of determining the blood pressure in the part of the artery subjected to compression loses its force completely in view of the fact now frequently recorded that the auscultatory and oscillatory criteria of the systolic pressure agree very closely; in my own experience, let me repeat, the agreement is exact. (See footnote at beginning of article.)

In conclusion let me say that I hope my remarks will not be taken as an attempt to discredit Dr. Kilgore's method of attacking the problem in hand, or of the conclusions he has reached. My main purpose has been to show (1) that those records that were sufficiently clear were read alike (within the limit of experimental error) by the same observer in two successive trials; (2) that the discrepancies appearing in the readings of different observers are probably greater than they would have been if each had been given the opportunity of making the records for himself under conditions obtaining in routine work; and (3) that our present criteria are by no means discredited by Dr. Kilgore's studies. But over and above all of this stands out the fact brought out by Dr. Kilgore, that without proper controls, readings of blood pressure records made by the method of continuous escapement may be, if not carefully made, worthy of only slight consideration.

The remedy would seem to lie (1) in using as the systolic criterion the change in form, with the paper moving at sufficient speed for this purpose; (2) in using the first *consistent* decrease in amplitude as the index to the diastolic; and (3) when in doubt, in controlling the readings made by the method of continuous escapement by readings made by the method of intermittent escapement.

It is regrettable that the only objective criteria we possess are sometimes difficult to make clear, and can be read only by exercising a certain amount of judgment. But until better objective methods can be

found, a goal toward which we are constantly striving, we must do the best we can with available methods though they may be fraught with large, in part known, inherent errors. These remarks, it may be added, apply with equal force to all methods now practiced of determining the blood pressure in man, for the record obtained by the graphic method is the resultant of all of the forces, both external and internal, acting to produce any of the criteria, and while some criteria may be clearer than others, they all are affected in much the same way by the changing forces. The nongraphic criteria may seem to be changed less, but from experience I can affirm that this is almost entirely the result of our inability to gauge the less objective criteria.

By observing proper precautions I am convinced, from my own experience, that the oscillatory criteria will be found to be quite as clear and as sharp as the auscultatory criteria, while the former possess the advantage, that is not without its value, of bringing to the attention of the observer the deficiencies of our blood pressure methods in *black and white* rather than in the form of *opinions*.

A QUANTITATIVE DETERMINATION OF THE PERSONAL FACTOR IN BLOOD PRESSURE MEASUREMENTS BY THE AUSCULTATORY METHOD

COMPARISONS WITH OTHER METHODS *

EUGENE S. KILGORE, HUGH K. BERKLEY, ALBERT H. ROWE AND W. H. STABLER
SAN FRANCISCO

Much has been written with regard to errors in human blood pressure measurements connected with such factors as rigid arterial walls, a too narrow cuff, etc., or the choice of the criteria for determining when pulse waves begin to pass under the cuff or when the diastolic pressure is reached; but heretofore little attention has been paid to the personal factor which operates in the identification of the various criteria. Since it is the large amount of individual judgment involved in "guessing" blood pressure by feeling of arteries, which has led to the general adoption of instrumental methods, it is important to inquire, in addition to other sources of error, how large this personal element may be when blood pressure instruments are used. Oscillatory criteria both for systolic and diastolic pressure, which have been advocated for use with several highly authorized instruments and which have been widely accepted as the most accurate and freest from subjective error, have been shown to invite surprisingly large variations in interpretation.[1] The ordinary palpatory method for systolic determinations has been investigated from this point of view[2] and the present report deals with similar experiments applied to the auscultatory criteria for both systolic and diastolic pressure. The experiments were in three groups:

GROUP 1.—The "Two-Arm" Experiments: This group consists of experiments by two of us (K. and S.) on sixty-one candidates for admission to the university, all healthy young men from 16 to 32 years of age. During the course of the required medical examination the blood pressure determinations were made with the subject lying quietly on his back on a narrow table. A 12 cm. pneumatic cuff was fitted to each arm, and both cuffs were connected with the *same* mercury U-tube manometer, which was overhung so as to be equally readable from both sides of the table. Both cuffs were inflated simultaneously

* From the Department of Medicine and the Students' Infirmary, University of California.

1. Kilgore, E. S.: Page 893, this issue.
2. Kilgore, E. S.: California State Jour. Med., March, 1914.

to a pressure above systolic pressure; and then, while the air from the combined system was gradually released through a slow outlet valve (the mercury falling about 2 mm. per second), one of us listened with a small open bell stethoscope over the artery a few centimeters below the cuff on the right arm while the other with a similar stethoscope ausculted at a corresponding point on the left arm. Each independently recorded by his reading of the manometer when the first sound was heard (systolic pressure), when the loud tapping sound finally changed to a dull distant one (the so-called "fourth phase" index of diastolic pressure), and when all sounds were lost ("fifth phase" index of diastolic pressure).[3] After two such procedures on one side we changed sides and repeated. Whenever the reading was not clear on account of extraneous noise or other accident no result was recorded; but if the observation was unhindered and the reading not clear on account of doubt about the definiteness of the criterion, a question mark was recorded in place of the reading. In these as well as in later experiments care was taken to avoid unconsciously signaling to one's partner when readings were made.

In this group the differences between the simultaneous readings of two observers obviously may be due to two causes: 1. Differences in hearing and interpreting the sounds and in observing the corresponding positions of the mercury column. 2. Actual differences in the blood pressure in the two arms or differences in the size or position of the artery or in the adjusting of the cuffs and stethoscopes. In order to separate these factors and ascertain the discrepancies referable to each of them the following group of experiments was undertaken.

Group 2.—The "One Arm" Experiments: In this group of experiments by K. and S., sixty-six of the same class of subjects were utilized. The procedure was exactly the same as in the first group with the exception that only one pneumatic cuff was used and but one stethoscope with a Y connection and two pairs of ear pieces. With the two branches of the stethoscope tube of equal length and the manometer equally readable to both observers, it is evident that both made their readings from absolutely identical data and that the discrepancies occurring in this series are referable solely to the first cause mentioned

3. Discussions of the merits of these "phases" as indices of diastolic pressure will be found in the following articles: Korotkoff: Mitth. a. d. mil. med. Akad. zu St. Petersburg, 1905, xi, 365; Fischer: Ztschr. f. diätet. u. phys. Therap., 1909, xii, 389; Lang and Mansivetona: Deutsch. Arch. f. klin. Med., 1908, xciv, 441; Ettinger: Wien. klin. Wchnschr., 1907, xx, 992; Gittings, J. C.: Auscultatory Blood-Pressure Determinations, The Archives Int. Med., 1910, vi, 196; Warfield, Louis M.: Studies in Auscultatory Blood-Pressure Phenomena, The Archives Int. Med., 1912, x, 258.

above. The discrepancies due to the second cause may then be determined by subtracting these results from the former ones.

GROUP 3.—The Control "One-Arm" Experiments: These were repetitions of the last group of experiments undertaken by the other two of us (B. and R.) as a control for the experiments of K. and S. The essential sameness of the results in the second and third groups counts toward the justification of the assumption that our results would correspond reasonably with those of others—an assumption formerly made by two of us in considering our results with the palpatory method.[2] The subjects in this group were twenty patients in the medical and surgical wards of the University of California Hospital. They were of both sexes and varied in age from 14 to 53 years and were without obvious cardiovascular abnormality. They were resting quietly on narrow hospital beds, and the manometer, which was a straight mercury tube and reservoir, was placed on a shelf over the bed. As an additional precaution against one observer's influencing the other, in these experiments a screen was placed over the bed between them, and the inflation and deflation of the cuff was controlled by an assistant.

To facilitate comparisons and avoid bewildering columns of figures, the results have all been reduced to percentages and expressed graphically in Figures 1 to 9. The curves are all according to one plan, which is to show the discrepancies between the readings of two observers[4] expressed in millimeters of mercury, and the percentage of instances in which each degree of discrepancy occurred. Millimeters of mercury are expressed along the abscissae and percentages of instances along the ordinates. Each curve except in Figure 7 extends both to the right and to the left of zero in order to show separately for each observer the instances in which his readings were the higher. Thus, a curve with long, lateral extensions and a blunt peak indicates that there were some large discrepancies and relatively few agreements, while a sharp tall peak with short lateral extensions signifies comparatively good results. A curve which reaches its highest point away from the zero pressure ordinate indicates a general tendency for one of the observers to choose higher reading points than the other. Perfect results would be represented by a peak reaching to 100 per cent. at zero mm. Hg.

In the first and second groups of experiments, in which a U-tube manometer was employed, there was a tendency for the readings and, hence, the discrepancies, to fall on the even numbers oftener than the odd, thus giving the plotted curve a "saw-edge" outline. Since irregu-

4. In one instance (Fig. 9) the marks of one individual made at two different times on duplicate graphic records are compared; and in Figure 7 the "fourth phase" and "fifth phase" readings of the same observers are compared.

larities of this dimension, when once their cause is recognized, have no further importance but interfere somewhat with the larger comparisons which it is desired to make, they have been "smoothed out," as will be observed, by combining values for the even and odd millimeters of mercury.

In the experiments in which the one divided stethoscope was used (Groups 2 and 3) the practical correspondence of the results by two pairs of observers is shown in Figures 1, 2, and 3. The solid lines show the differences between the readings of K. and S. and the dotted lines the same for B. and R.

In the systolic determinations (Fig. 1) the differences in the second group vary from zero to 12 mm. Hg and average 1.42; in the third group from 0 to 10 mm. Hg, average 1.58.

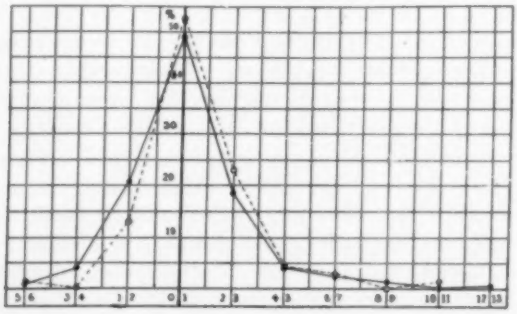

Fig. 1.—Close correspondence shown in results of two series of "one-arm" systolic readings. Solid line, descrepancies of K. and S.; dotted line those of R. and B. The cases in which K's readings and those of R. were higher than those of their partners are to the left side; to the right are the cases in which S's and B's readings were higher.

In the use of the change of sound or "fourth phase" diastolic criterion (Fig. 2) discrepancies in the second group occur as high as 15 mm. Hg and average 2.6; in the third as high as 9 mm. Hg, average 2.47.

In locating the points of sound disappearance (Fig. 3) K. and S. recorded points as far apart as 17 mm. Hg, and their average difference was 2 mm.; B. and R. had an average difference of 1.76 mm. Hg and once 10 mm.

It will be seen that there is essential uniformity in the results of the two pairs of observers both in the range and distribution of the discrepancies and in the averages. In view of this correspondence it is assumed that the showings made by K. and S. in the first and second groups of these experiments, as well as in their previously

reported experiments with the palpatory method[2] represent the errors referable to the personal factor which ordinarily prevail in the use of these methods. In the following analysis, therefore, only their results are included.

The Systolic Readings.—Taking as we did, as the index of systolic pressure, the first sound heard while air was escaping from the cuff, none of these points was classed as doubtful in any of the series of experiments. The beginning of the sounds was usually very clear cut,

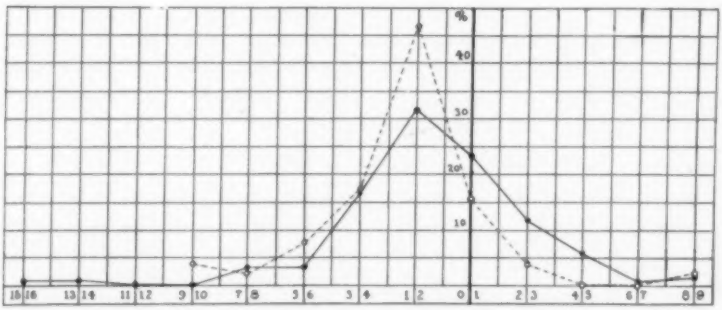

Fig. 2.—"Fourth phase" diastolic readings. Arrangement same as in Figure 1, except that the higher readings of B. are to the left and those of R. to the right.

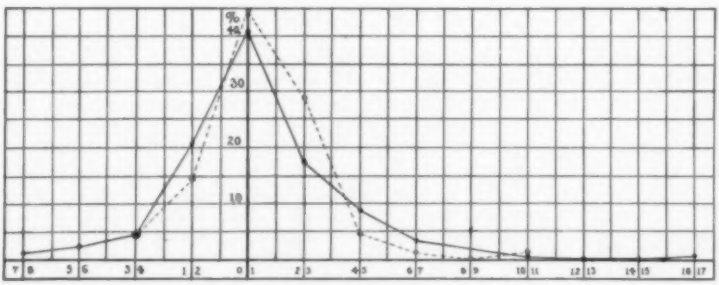

Fig. 3.—"Fifth phase" diastolic readings. Arrangement same as in Figure 1.

and we were surprised by some of the large discrepancies in our records. It seems probable that some of the wide variances here as well as in the diastolic determinations were due to mistakes of ten points in reading the manometer.

As previously indicated, disagreements in the second group of experiments in which but one cuff and one stethoscope were used can only be accounted for by errors in reading the manometer and in recognizing the criterion. These are shown in the solid line in Figure

4. The dotted line shows the discrepancies of the same observers when two pneumatic cuffs and two stethoscopes were used. The figure shows that in the "two-arm" experiments fewer of the discrepancies are near zero and more of them have higher values than in the "one-arm" group; the average in the former case being 3.54 mm. Hg and in the second 1.42. The difference of 2.12, as explained above, is a measure of the added effect of using both arms of the subject and applying two cuffs and two stethoscopes.

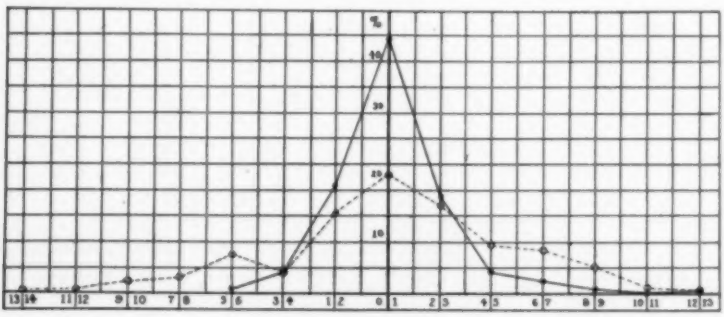

Fig. 4.—Systolic readings. Relation shown between discrepancies in simultaneous readings of K. and S. using one stethoscope (solid line) and the discrepancies of the same observers in the "two-arm" experiments (dotted line). The higher readings of K. are to the left, those of S. to the right.

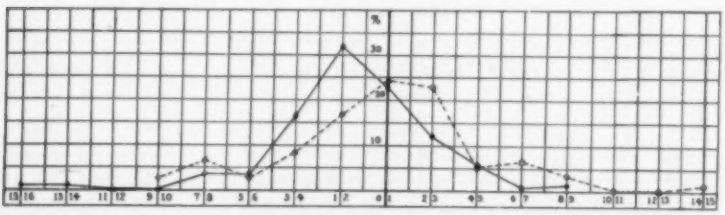

Fig. 5.—"Fourth phase" diastolic readings. "One-arm" and "two-arm" determinations compared as in Figure 4.

These figures are based on 236 determinations (by each of two observers) in the sixty-one subjects of the first group, and 282 determinations on the sixty-six subjects in the second group. None of the readings were classed as doubtful.

The Diastolic Readings by the "Fourth Phase" Index.—Figure 5 is arranged in the same way as Figure 4 to show the comparative results when one stethoscope and when two were used. The average discrepancy in the one-stethoscope experiments was 2.6 mm. Hg, in the

first group 3.09, a difference of 0.49 mm. Hg. The smallness of this difference is partly explainable by the tendency of K. in the second group of determinations to choose a point 1 or 2 mm. higher than S. did; a tendency not observed in the first group of experiments and clearly due to a slight change during the course of the experiments in the habit of either S. or K. in interpreting the criterion.

Out of 232 attempted "fourth phase" readings in the first group only seventy-nine were accepted for the above analysis, the remaining 153 (66 per cent.) being classed as "doubtful." These occurred in fifty-five of the sixty-one subjects. Similarly among the 273 attempted readings in the second group 143 or 51 per cent. (occurring in fifty-seven out of the sixty-six subjects) were rejected as "doubtful."

"Fifth Phase" Diastolic Readings.—In the first group there were 228 of these readings and in addition four marked questionable; in the second group 260 readings and twelve which were discarded as doubtful.

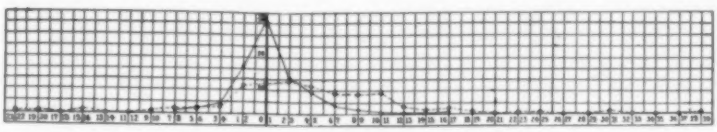

Fig. 6.—"Fifth phase" diastolic readings. "One-arm" and "two-arm" determinations compared as in Figure 4.

Figure 6 shows that in the one-stethoscope experiments the results are comparable with those for the other criteria, and that the two observers took the higher readings about equally.

In the "two-arm" experiments the discrepancies are much larger than usual on both sides of the figure, which suggests that in these subjects at least the disappearance of sounds is particularly subject to variation from sources other than blood pressure, such, for example, as anatomic variations or variations in the adjustment of the apparatus.

The curve also shows, however, that a preponderance of the higher readings was made by S., that is, K. more often followed the sounds to a lower level. Since this difference does not appear in the "one-arm" experiments, the only possible explanation is that here again, during the course of the experiments, one at least of these observers changed his habit of interpreting the criterion.

Relation Between "Fourth Phase" and "Fifth Phase" Readings.—An opportunity is here afforded to compare the difference between "fourth phase" and "fifth phase" readings in two slightly different groups of subjects, hospital patients and young men students. Figure

7 shows this comparison in the two groups of experiments which were exactly parallel (the "one-arm" experiments) on the two classes of subjects. In each group the readings of both observers have been included; the solid line represents the differences between fourth and fifth phase readings when the students were used as subjects by S. and K., the dotted line represents the same differences in the readings of B. and R. on hospital patients. It will be noted that the greatest differences between these two diastolic indices occurred among the deter-

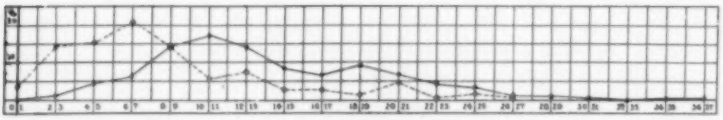

Fig. 7.—Relation shown between "fourth phase" and "fifth phase" diastolic readings in the "one-arm" test of K. and S. on students (solid line) and of B. and R. on hospital patients (dotted line).

minations on students; the average difference was considerably higher in this group, 13.5 mm. Hg as compared with 8.5 mm. Hg in the measurements on hospital patients. In a few instances the two indices were so near together as to be practically inseparable.

COMPARISON WITH OTHER METHODS

A. The Palpatory Method: For systolic blood pressure, the conditions affecting the "two-stethoscope" experiments in this series were practically identical with the conditions in the palpatory systolic

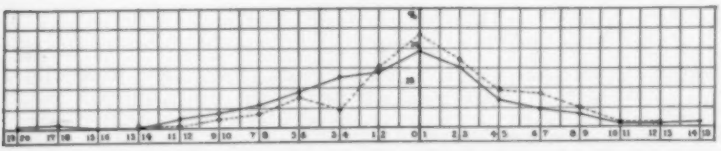

Fig. 8.—Systolic readings. Close correspondence shown between the discrepancies of the palpatory method (solid line) and the auscultatory method in the "two-arm" determinations of the same observers. The cases in which K's readings were higher are to the left, those of S. to the right.

measurements previously reported for the same two observers,[2] so that the two methods may be directly compared. This comparison is shown in Figure 8, the solid line representing the discrepancies of K. and S. with the auscultatory method and the dotted line the same with the palpatory method. The figure shows that although the auscultatory discrepancies in the region of zero have a slightly higher percentage and never on the extreme sides of the curve quite equal the largest

palpatory discrepancies, still the differences are relatively small and well within the limits of experimental variation. In fact, in view of the tendency illustrated above for observers from time to time to change their habits of interpreting the criteria, these two curves approach coincidence as nearly as could be expected if either of these groups of experiments were repeated. The difference between the average discrepancies (3.54 mm. Hg in the auscultatory and 4.08 mm. Hg in the palpatory) is small in comparison with other variables in series as small as these.

We have not investigated the personal factor in the use of Strassburger's palpatory diastolic criterion, as it seemed hopelessly great.

B. The Oscillatory Method: In another article[4] experiments are being reported concerning the personal factor in the interpretation of the oscillatory criteria. The conditions of those experiments do not permit an exactly parallel comparison with our tests of the auscultatory and palpatory methods; the nearest that can be made is with the "one-arm" auscultatory tests, in which the conditions are favorable to the oscillatory indices in four respects: (1) The personal factor connected with the reading of the manometer is not included in these oscillatory results. Further, in contrast to the conditions of actual practice, the oscillatory readings were made (2) on completed tracings, (3) without the need for haste, and (4) without the necessity of dividing the attention between them and the manometer.

The two subjects whose descriptions of the oscillatory systolic criterion seem most alike are "A" and "D." In seventy systolic readings which escaped criticism or expression of doubt by either of them their differences range from zero to 20 mm. Hg and average 2.91 mm. Hg, which, it will be remembered is about twice the average discrepancy in either of the two series of "one-stethoscope" experiments. In view of the conditions, previously mentioned, it is to be presumed that this average would be materially increased in actual practice by these observers, and the comparative showing made by them is decidedly unfavorable to the sudden increase in amplitude or "principle of von Recklinghausen," which they followed. That the ordinary palpatory index of systolic pressure would stand with the auscultatory criterion in the same favorable comparative light if it could be subjected to the "one-arm" test may be assumed from the close correspondence which we found to exist between it and the auscultatory method in the "two-arm" experiments.

The "change in form," the other systolic oscillatory criterion proposed by Erlanger,[5] is not included in these comparisons, because the

5. Erlanger, Joseph: Am. Jour. Physiol., 1908, xxi, 24.

evidence concerning the personal factor in its use was not considered conclusive. Also Erlanger's method of "intermittent escapement"[6] for systolic and diastolic determinations was not the subject of experiment.

In the second part of the article on the oscillatory indices referred to above the average discrepancy in a series of diastolic comparisons is 5.4 mm. Hg, which, it will be remembered, is approximately two or three times as great as the average for either fourth or fifth phase determinations in both of our groups of "one-arm" experiments (fourth phase discrepancies of K. and S. averaged 2.6 mm. Hg, of B. and R. 2.47; fifth phase discrepancies of K. and S. 2, of B. and R. 1.76). We have taken our worst showing, the "fourth phase" readings of K. and S. for comparison with these oscillatory diastolic discrepancies; the dotted line in Figure 9 represents the oscillatory results, the

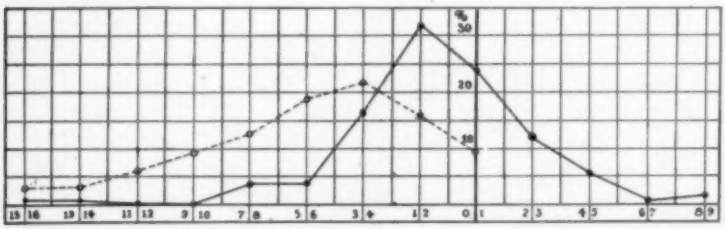

Fig. 9.—Diastolic readings. "Fourth phase" auscultatory discrepancies in K's and S's "one-arm" experiments (solid line) compared with discrepancies in rereading by the same observer ("C") diastolic points in graphic oscillatory records (dotted line). K's higher readings are to the left. The cases in which C's later readings were higher than his earlier ones are charted to the left. The dotted line does not appear to the right, as earlier readings were never higher than the later ones.

solid line the auscultatory. In judging this comparison it must be borne in mind that the oscillatory readings were performed under the four conditions of unnatural advantage mentioned above, that is, conditions which are not enjoyed in practice. Moreover, in this instance, the oscillatory method was favored in another and specially important item in that the marks of but one individual ("C") instead of two were compared—an advantage which is possible only to graphic records, and which was obtained by submitting for marking a second series of photographic prints of tracings identical with a series which had been marked by the same observer eleven months previously.

Figure 9 also shows a pronounced change of habit in interpreting the oscillatory diastolic criterion on the part of "C," his higher readings without exception being found on the second set of tracings.

6. Erlanger, Joseph: Rep. Johns Hopkins Hosp., 1904, xii, 53.

DISCUSSION AND CONCLUSIONS

These investigations are practically limited in scope to a single source of error in blood pressure measurements, namely, personal differences between observers in the identification of auscultatory systolic and diastolic criteria and in reading the mercury manometer. In the "two-arm" experiments, however, anatomic causes of discrepancies or actual differences in blood pressure between the two arms of the subjects could not be ruled out.

So far as our experiments go, there is little to choose in point of definiteness between the common palpatory systolic index and the newer auscultatory criterion. Our findings, therefore, while not including tests of a sufficient number of observers to be conclusive, do not substantiate the impression widely existing at present that the stethoscope offers a much more definite and reliable systolic blood pressure index than that formerly used. While it is not within the scope of this paper to consider at length the relative merits of methods, it may be pointed out that an intelligent choice between the auscultatory and palpatory methods for systolic readings will involve consideration of the following points: (a) the convenience of the palpatory method; (b) its freedom from interference by extraneous noises; (c) the fact that most of the blood pressure data in clinical literature refer to the palpatory method; (d) the fact that in certain subjects the auscultatory readings cannot be made, and that in certain others they are lower than can be obtained by palpation; (e) the fact that, whereas the auscultatory readings are commonly higher than the palpatory, the latter themselves have been found to be somewhat too high in the few instances in which they have been controlled in human subjects by direct manometric measurements.[7]

The commonly used oscillatory indices, according to our analyses, invite much greater vagaries in interpretation than either the palpatory or auscultatory method for systolic readings or the auscultatory for diastolic readings.[8] This finding, if it receives confirmation, will be particularly important in view of the wide acceptance of the

7. Müller and Blauel: Deutsch. Arch. f. klin. Med., 1907, xci, 517; Volhard: Verhandl. d. Cong. f. inn. Med., 1909, xxvi, 200; Dehon, Dubois and Heitz: Compt. rend. Soc. de biol., 1912, lxxii, 789.

8. Part of the discrepancies in the use of the oscillatory method were attributable to individual differences in the understanding of the criteria to be followed. This factor, we believe, has not appreciably influenced our results with the palpatory and auscultatory methods. The palpatory systolic criterion used by some, however, is the "fully developed" radial pulse wave rather than the first one to be felt. An index which depends on the relative amplitude of pulse waves is obviously much less definite than the appearance of a wave where none before existed; and for this reason as well as because it is the more commonly used criterion, we have accepted the first wave to be felt, although certain theoretic considerations favor the fully developed waves.

oscillatory method as the most "objective," hence the freest from personal factor errors, and its use on this account as a standard or means of "checking up" other methods. Reasons have been presented[1] for the special condemnation of methods in which the attempt is made to use the oscillatory indices with instruments which do not supply graphic records.

Notwithstanding their favorable comparison with the oscillatory method, both of the auscultatory diastolic criteria which have been proposed leave much of definiteness to be desired. This is shown in our "fourth phase" determination by the large number of readings which were rejected because the sound changes were not considered abrupt enough to afford clear readings, as well as by the comparatively large number of higher discrepancies in the comparisons which were made.

Our greatest differences in simultaneous readings occurred in the "fifth phase" experiments, in which, in one instance, we differed by as much as 38 mm. Hg. Particularly in our "two-arm" experiments the number of instances in which we agreed was small. These results we believe would have been modified decidedly for the better if all our subjects had been of the ordinary hospital class. For, in examining the students, who as a rule are more or less excited by the novelty of the medical examination, we have been impressed with the unusually gradual and protracted waning of the artery sounds before their final disappearance. In accord with this impression is our finding of a considerably greater average difference between the fourth and fifth phase readings in the student measurements than in those made on hospital patients. Our experiments on the students indicate better agreement among the fourth phase determinations than in the fifth phase; in the experiments on hospital patients, however, the fifth phase determinations showed a slightly smaller average discrepancy.

In conclusion it should be stated that the differences between blood pressure readings in these experiments would be somewhat lessened if as a basis for comparison the highest reading by each observer on a case or the average of several readings were used instead of individual readings. Better results might also be obtained by combining methods, using one as a check against another. The comparison of single simultaneous readings, however, while it makes for ourselves a somewhat poorer showing than we may hope exists in our actual practice, is the direct way to determine disagreements of observers, and it is obviously the best way to compare results obtained by different methods.

THE FRACTIONAL METHOD OF BLOOD PRESSURE DETERMINATION—A CONTRIBUTION TO THE STUDY OF BLOOD PRESSURE IN CARDIAC ARRHYTHMIAS *

EUGENE S. KILGORE
SAN FRANCISCO

Among the sources of error in human blood pressure measurements an important factor, which has received comparatively little attention, is variation in pressure between individual pulse waves or between groups of them. It is well known that undulations in systolic and diastolic pressure occur commonly in normal persons with each respiration or at somewhat longer intervals; and among the cases of cardiac arrhythmia, there may be the widest pressure differences even between consecutive pulse waves. The custom of clinicians to accept the average or the highest of several determinations, or simply the first reading made, while tolerably meeting the needs of practice among cases with regular heart action, amounts to the roughest kind of guess-work in cases of marked arrhythmia. Mackenzie[1] gave up the attempt to measure blood in cases of auricular fibrillation. It will be shown, however, that notwithstanding the great differences between individual waves in these cases, the average pressure from minute to minute may be remarkably stable; and that the determinations, though not expressible as single figures, may have as much accuracy as the ordinary clinical methods will yield in normal cases.

It will be unnecessary here to discuss the numerous attempts which have been made to obtain graphic records showing quantitatively the rapid changes in human arterial pressure. Suffice it to say that up to the present the sphygmographs and plethysmographs used as receivers have been beset with technical difficulties which make them not only inconvenient, but uncertain in their results.[2]

Another group of endeavors has had more limited aims, such as:

a. To show the highest and lowest systolic pressures in a series of irregular beats, by noting the cuff pressure at which no beats come through and that at which all come through.[3]

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* From the Department of Medicine, University of California.

1. Mackenzie: Heart, 1911, ii, 283.
2. Weber: Arch. f. Anat. u. Physiol., 1913, Physiol. Abt.
3. Wybauw: Ztschr. f. klin. Med., 1911, lxxiii, 214.

b. To show qualitatively variations above or below a known systolic pressure by noting the appearance and disappearance of the "change in form" in an Erlanger sphygmomanometer curve.[4]

c. By the method of intermittent escapement and the use of the graphic oscillatory criteria, to show the general level of systolic and diastolic pressures when there is variation among the beats.[5]

d. To compare the number of beats coming through one radial artery with those coming through the other when varying degrees of pneumatic pressure are applied to one arm, using a sphygmograph on each wrist for registering the beats.[6]

Observations similar to the last mentioned were made by James and Hart,[7] but without the use of instruments other than the ordinary clinical blood pressure apparatus. Their method was to count the heart rate by auscultation of the precordia, and by palpation of the radial artery the rate without arm compression and also with different degrees of compression by the pneumatic cuff. From these observations they could state approximately: (1) The number of beats per minute which fail to reach the periphery as palpable waves (the so-called "pulse deficit"), and (2) the number per minute which have a systolic pressure of 140 mm. Hg, 130, 120, and so on.[8] The pressure variation among the pulse waves in the arm they designate the "relative deficit." What they call the average pressure is obtained by multiplying, for example, by 140 the number of beats per minute which they considered to have that pressure, by 130 the number with that pressure, and so on; then adding all these products and dividing the sum by the heart rate as counted at the apex. They did not apply the procedure to diastolic pressures.

A simple method such as this is attractive on account of the non-requirement of machinery other than the ordinary blood pressure apparatus. The only advantages which could be claimed for one of the graphic methods would be the doubtful one of increased accuracy in identifying and counting the waves which passed under the compressing cuff, and the possibility of registering simultaneously the rate of the unobstructed pulse. The pulse rate would, of course, be needed for correct interpretation of the results if it changed materially from minute to minute. That such is not the case, however, in cases of auricular fibrillation, where this method finds its greatest usefulness, is the experience of James and Hart and of myself. Moreover, in the

4. Erlanger and Festerling: Jour. Exper. Med., 1912, xv, 370.
5. Erlanger: Johns Hopkins Hosp. Rep., 1904, xii, 53.
6. Silberberg: Brit. Med. Jour., April 6, 1912.
7. James and Hart: Am. Jour. Med. Sc., January, 1914, p. 63.
8. A slight error in these calculations will be referred to later.

method of plotting the results here proposed, any noteworthy change of the pulse rate or of the general run of pressure during the experiment would at once become evident as a distortion of the curve. The essential "smoothness" of such a curve is evidence of the constancy of the circulatory conditions during the experiment.

A method differing from that of James and Hart in two important particulars (the interpretation of systolic determinations and the inclusion of diastolic readings) was initiated in the University of California Hospital about one year before their publication, and the illustrations herewith presented are taken from the hospital records of the last two years. We have designated it the *fractional method* because of its obvious similarity to the fractional procedures of chemistry, bacteriology, etc. It will best be described by examples:

Section 1.—Cases in which the Lowest Systolic Pressures are Above the Highest Diastolic Pressures. Medical Case 8243, admitted Nov. 13, 1914; diagnosis, mitral stenosis, auricular fibrillation. Although the heart was absolutely irregular, practically every beat had a corresponding radial pulse. With circular compression of 150 mm. Hg applied by a 12 cm. pneumatic cuff to the upper arm, no waves were felt in the radial artery of the same side during half a minute. After emptying the cuff and resting the arm a few seconds, the pressure was again raised and held for one half minute at 145 mm. Hg. During this time two waves were felt at the wrist. Then there was another rest of the arm, inflation of the cuff, and half minute count of the waves which were able to lift 140 mm. Hg, and so on down to 110 mm. Hg, which obstruction all the waves were able to pass.

For the fractional determination of diastolic pressure a stethoscope was placed over the artery a few centimeters below the cuff, and with further similar decrements of cuff pressure, the numbers of arterial sounds heard in half minute intervals were counted (i. e., the "fifth phase"[9] or sound disappearance criterion was followed).

The results are shown graphically in Figure 1, in which the dots represent the rate per minute (indicated by the corresponding figures on the base line) of waves which pass under a given degree of pressure in the pneumatic cuff (indicated by the corresponding figures at the left), and where the circles in a similar way indicate the counts of sounds. The connecting lines, it will be noted, are drawn with the purpose of representing the probable truth rather than with absolute faithfulness to the dots and circles: i. e., *small* irregularities have been "smoothed out." This undoubtedly increases the accuracy of the lines (provided of course that enough counts have been made to bring the

9. Gittings: THE ARCHIVES INT. MED., 1910, vi, 196.

dots and circles approximately in line), since it is what happens when such curves are based on much larger numbers of counts. The purpose of this paper being primarily to describe the method, in the interest of clearness and simplicity in the figures which follow only the smoothed out lines are shown.

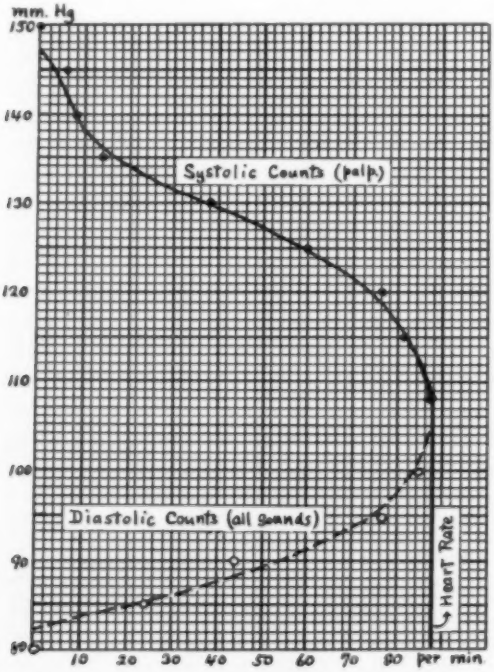

Fig. 1.—Showing the relation of systolic and diastolic pressures in a typical case of auricular fibrillation in which the diastolic pressure of one cycle never exceeds the systolic pressure of another. In this as well as the following figures the numbers at the left indicate millimeters of mercury pressure in the pneumatic cuff; those at the bottom the rate per minute of beats counted in various ways. The upper line here represents the results of palpatory systolic counts, the lower line fifth phase diastolic counts.

Figure 1 may be better understood if it is imagined that the 88 pulse waves in a minute are represented by sticks with lengths proportional to the systolic pressures, and that these sticks are stood up in the order of their lengths, the longest on the left and the shortest on the right. Their tops would form the upper curve in the figure. A similar set of sticks representing diastolic pressure would form the lower curve if the longer ones were placed on the right.

It will be seen that the systolic pressure varies between 110 and 145 mm. Hg, and that its average is in the neighborhood of 125 to 130. To continue the illustration of the sticks, the average systolic pressure would be represented by their average length, which would be obtained by dividing the sum of their lengths by their number. The average length of 88 equally spaced ordinates dropped from the systolic curve in Figure 1 is about 129.

An approximately correct average can be obtained with less labor by dealing with groups rather than points on the line representing single waves. For example, according to the figure, there were six waves per minute with a pressure between 145 and 150. These six may all be considered to have a pressure half way between the two limits: i. e., 147.5 mm. Hg. In this way the complete calculation would be as follows:

(*a*)	(*b*)	(*c*)*	
6	0 =	6.	$6 \times 147.5 =$ 885
8	6 =	2.	$2 \times 142.5 =$ 285
14	8 =	6.	$6 \times 137.5 =$ 825
38	14 =	24.	$24 \times 132.5 = 3{,}180$
60	38 =	22.	$22 \times 127.5 = 2{,}805$
76	60 =	16.	$16 \times 122.5 = 1{,}960$
82	76 =	6.	$6 \times 117.5 =$ 705
88	82 =	6.	$6 \times 112.5 =$ 675

$11{,}320 \div 88 = 128.6$ = average systolic pressure.

* In the figures shown herewith the numbers on the base line correspond to the figures in column *a* in the above tabulation; i. e., they represent total numbers of waves felt or sounds heard at the corresponding cuff pressures. For some purposes it would be an advantage to construct curves in which the base line figures represented the quantities in column *c*, i. e., the number of beats which have a certain pressure. In such a figure taken from a normal case there would be two narrow curves separated by the amount of the pulse pressure, while if it were from a very irregular case the diastolic and systolic curves might overlap. The work of constructing these additional curves is unnecessary if it is remembered that their lateral extent would depend on the slope of the curves here employed. In the figures herewith, the more uniform the pressure of the beats the more nearly horizontal the lines, and the more variable the pressure the more sloping the lines.

It will be noted that this average differs by only about one-half millimeter from that obtained by measuring the whole 88 ordinates. In the averages calculated by James and Hart[7] only half as many multiplications were made, i. e., waves were considered together which were within limits 10 mm. Hg apart instead of 5 mm. Undoubtedly the additional error introduced in this way is still well within the limits of accuracy of the method as a whole. A mistake of approximately 5 mm. Hg, however, appears throughout their figures, which is unnecessary and easily corrected. For example, a group of beats which ranged in pressure from 130 to 140 mm. Hg they counted as

having a pressure of 130. On the chances, the average pressure of this group would be near the midpoint or 135 rather than the lower limit of 130.

The diastolic pressure is calculated from the lower curve in Figure 1 in the same way as systolic pressure, thus:

(*a*)	(*b*)	(*c*)*	
24 —	0 =	24.	24 × 82.5 = 1,980
44 —	24 =	20.	20 × 87.5 = 1,750
76 —	44 =	32.	32 × 92.5 = 2,960
84 —	76 =	8.	8 × 97.5 = 780
88 —	84 =	4.	4 × 102.5 = 410

7,880 ÷ 88 = 89.5 = average diastolic pressure.

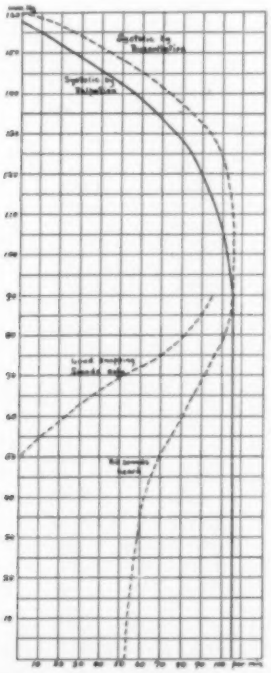

Fig. 2.—Showing the relation between palpatory (solid line) and auscultatory (broken line) systolic readings, and between fourth phase and fifth phase diastolic readings. From a case of hyperthyroidism and auricular fibrillation.

Obvious variations of the technic are to use the auscultatory method for systolic determinations and the "fourth phase"[9] or sound transition index for diastolic readings; i. e., to count all the arterial sounds heard instead of the pulse waves felt in the systolic region, and in the diastolic region to include in the counts only the loud staccato notes and omit the dull distant ones. Figure 2 shows

side by side the results obtained by the use of the palpatory and auscultatory criteria for systolic pressure, and of sound transition and sound disappearance for diastolic pressure. It will be seen that in these fractional determinations there is present the usual excess of auscultatory over palpatory systolic readings, and of "fourth phase" over "fifth phase" diastolic readings. The case from which this was obtained was one of auricular fibrillation with hyperthyroidism. The pulse approached the Corrigan in type, which accounts for the persistence of many of the arterial sounds during little or no cuff pressure.

For purposes of comparison it is desirable to use the same criteria for the determinations in these cases of arrhythmia as in ordinary cases. For general use in systolic determinations our choice has been the palpatory criterion, on account of its convenience, and we believe, equal or greater reliability.[10] For diastolic readings we ordinarily use whichever auscultatory criterion seems the clearer, and indicate in the record which is used. In fractional determinations the "fifth phase" criterion is usually preferable, as it relieves the observer of the necessity of differentiating between qualities of sounds, and also takes away the danger of confusing sounds above the "fourth phase" with those below it. (In the second and third phases the murmur is frequently indistinct and the sounds very dull and distant.) A few cases, such as aortic insufficiency, will have audible sounds over the arteries with little or no compression; these necessitate the use of the sound transition criterion. Unless otherwise stated it is understood that the remaining observations here referred to were all obtained by the use of the palpatory index for systolic pressure and the disappearance of sounds for the diastolic.

Section 2.—Cases in which the Diastolic Pressure of Some Beats Exceeds the Systolic Pressure of Others. Figure 3 (Case 9229, May 21, 1915) illustrates this condition. Instead of coinciding as in Figure 1, the lines representing, respectively, systolic and diastolic pressure intersect; i. e., apparently the diastolic pressure of some cycles exceeds the systolic pressure of others. When this is so, it is necessary to make certain allowances in interpreting the diastolic counts with the higher cuff pressures, for the reason that not all of the silent waves are so because their diastolic pressures are above that in the cuff; some are not heard because they fail entirely to pass the cuff. An example in Figure 3 is the count of sounds when the cuff pressure was 115 mm. Hg. The figure shows that the rate of these sounds was 58 per minute, which would mean, according to the

10. Kilgore: A Quantitative Determination of the Personal Factor in Blood Pressure by the Auscultatory Method, THE ARCHIVES INT. MED., this issue, p. 893.

usual interpretation, that fifty-eight waves per minute had a diastolic pressure lower than 115 mm. Hg. But from the palpatory systolic counts it is known that even less cuff pressure was able to hold back entirely some of the smaller waves (at least so far as the finger could determine), and therefore, wrongfully for our results, exclude them from the stethoscope counts. The upper end of the diastolic line, therefore, needs to be corrected by bending it toward the right.

To determine the amount of correction to be made in the diastolic line, it is first necessary to make some of the systolic readings by auscultation as well as by palpation and to correct the lower end of the auscultatory systolic line (where beats may be missed on account of high diastolic pressure as well as on account of low systolic pressure) in accordance with the palpatory readings; i. e., so that the vertical

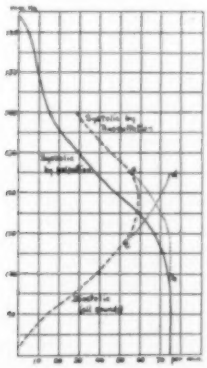

Fig. 3.—Showing the correction and extension of the upper end of the diastolic line in cases in which the diastolic pressure of some cycles exceeds the systolic pressure of others. Case of premature contractions followed by alternating pulse waves.

distance between the two lines shall be everywhere the same as at the higher pressure levels.[11] The dotted portion (*ab*) of the systolic auscultatory line in Figure 3 has been thus corrected. The difference between each point in this corrected auscultatory systolic line and the heart rate per minute, equals the number of waves per minute which are silent at that cuff pressure on account of their lower systolic pressures, and is therefore the number of beats to be added in order to correct the diastolic line at the corresponding pressure. For example,

11. It is assumed that the relation between palpatory and auscultatory systolic readings is about the same at different pressure levels. This probably is not strictly true, but it is certain that any error from this source is small and well within the limits of accuracy of the method as a whole.

at pressure 110 this corrected auscultatory systolic line indicates 72 per minute, which is three short of the heart rate of 75. Three beats are therefore added to the diastolic line at pressure 110. Similarly at 115, five beats are to be added, and so on. The dotted portion (*cd*) of the diastolic line in Figure 3 was constructed in this way.

From these corrected lines the average systolic and diastolic pressures may be calculated as described in Section 1. The cases in which it is necessary thus to correct the diastolic line are comparatively few, as even in very marked cases of arrhythmia the diastolic line does not intersect the systolic line until both are at or near their limit. And when they cross only slightly before this, the diastolic line can be roughly corrected by "free hand exterpolation" within the limits of accuracy of the method.

Section 3.—Cases in which without Brachial Compression Some of the Heart Beats Fail to Reach the Radial Artery as Palpable Waves. Cases with abortive beats[12] form a large proportion of the patients with absolute arrhythmia in the stage of decompensation, and a considerable number of patients with premature contractions. Clinically there is no method at present of measuring the exact pressure of these small beats, but they can be placed between certain rough limits. Those which produce both first and second heart sounds may be assumed to have opened the semilunar valves[13] (presumably both pulmonic and aortic), and therefore to have exceeded the diastolic pressure of the preceding beat. Isolated first heart sounds, on the other hand, may be taken to indicate beats with systolic pressure below the existing diastolic pressure in the aorta.

Unfortunately the diastolic pressure as a limit is itself quite variable in most of these cases (in Figure 3, for example, it varies from 82 to 125 mm. Hg). Since, however, a prominent factor in causing

12. The difference between the apex and the radial counts has been referred to as the "pulse deficit." "Abortive beats" has seemed to us a better term because its meaning is clear and it directs attention to the heart, in respect to which these beats are important, rather than to the pulse, where they are not so important. Even in the presence of many abortive beats, there may be an ample number of large beats for the needs of the peripheral circulation; and from this point of view it seems not quite appropriate to speak of the small beats as a deficit. Indeed they might with less impropriety be referred to as a surplus.

13. Professor Joseph Erlanger has verbally called my attention to the possibility of second heart sounds occurring without a preliminary opening of the semilunar valves. It is quite conceivable that the systolic pressure on the side of the ventricle may at times be sufficient partially to relax the tension on the valves without opening them, and that their return to the tense position at the beginning of diastole may produce a sound. Whether or not this actually takes place would of course be difficult to prove; if it does, the sounds thus produced might be expected to be less intense than the second sounds of the effective beats.

these small ventricular discharges (or attempted discharges) is insufficient ventricular filling, due to the shortness of the preceding diastole, and since it is usually the long pauses that bring about the low diastolic pressures, it may be inferred that these abortive beats usually happen during relatively high diastolic pressure. Occasionally, particularly in some cases of premature contractions, several small beats follow each other in rapid succession; the output of these beats may be negligible, and arterial pressure during the short interval may therefore decline rapidly, and the last beat or two may fall in instants of relatively low diastolic pressure. If desired, a cardiographic record or a record of

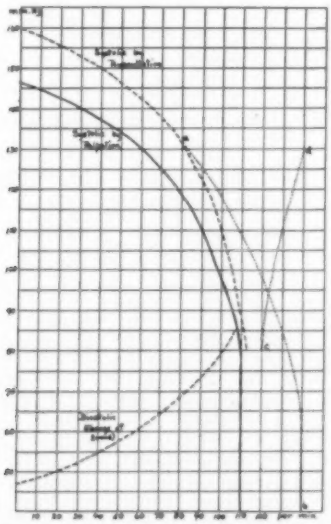

Fig. 4.—Showing the correction of the lower end of the systolic line to represent abortive beats. Hyperthyroidism with auricular fibrillation.

heart sounds could be used for studying the diastolic periods and the probabilities that a certain proportion of the beats would occur during high or low diastolic pressure.

Figure 4, which is from a case of myocarditis with premature contractions (No. 7747), shows that with a cuff pressure of 80 mm. Hg all the waves were felt which could be felt with no cuff pressure (110 per minute); and yet each minute there were thirty additional heart beats which could not be felt at the wrist, but which, the sounds were assumed to indicate (second sounds always present), discharged blood into the aorta against a diastolic pressure of 50 to 80 mm. Hg. And, since these abortive beats did not occur in series, it may be assumed that the systolic pressure of the weakest of them

was probably over 65 mm. Hg. Moreover, it is highly probable that their pressures varied as did those of the larger beats, and that, therefore, if measurable they would be represented by a line approximately in the position of the dotted line *ab* in Figure 4; i. e., a continuation of the auscultatory[14] systolic line by a more or less symmetrical curve up to the full heart rate (140) and the presumable pressure of the weakest beats (65 mm. Hg). Fortunately, in the region of low pressure this curve is naturally bending so little that the exact location of the point of lowest systolic pressures, which, as explained above, is quite conjectural, makes comparatively little difference in the placement of the line.[15]

14. The fact that systolic readings by palpation are usually somewhat lower than those by auscultation presumably indicates that the auscultatory method is more delicate for determining the pressure of waves which can pass the cuff. And, since in this rough calculation of the pressure of the abortive beats naturally no margin is allowed for failures to demonstrate them, the line representing them should be a continuation of the auscultatory rather than the palpatory systolic line.

15. The line *ab* representing the systolic pressure of the abortive beats in Figure 4 extends up as high as 130 mm. Hg. A natural question will be why beats with such a pressure cannot be felt in the radial artery with no brachial compression. It is a frequent observation that patients with systolic pressure as low as 50 or 60 mm. Hg (shock, etc.,) have distinctly palpable pulse waves. The answer of course is that the palpability of pulse waves depends not on their absolute pressure, but on the relative increment of pressure, which in turn depends very largely on the volume discharged from the ventricle. That is, with suitable allowances for distensibility of artery walls, interference of surrounding tissues, etc., the case comes under Weber's psychological law (Wagner's Handwörterbuch, Braunschweig, 1846, iii, Abt. 2, p. 511), which is to the effect that for equal increments of sensation, increasing increments of stimulation are necessary. The small pressure increments presumably also prevent many beats with high absolute pressure from giving rise to sounds below the cuff.

The line representing abortive beats in cases other than absolute arrhythmia may obviously have a different type of curve, depending on the conditions. For example, in a case with regular effective beats and regularly recurring abortive premature contractions, the latter might all have about the same pressure, so that they would have to be represented by a nearly horizontal line. In order to locate a rough limit for the pressure of the abortive beats, it would be necessary, as in the case illustrated by Figure 4, to determine the diastolic pressure which they did or did not exceed (presence or absence of second sounds). This could be done approximately by comparing the electrocardiogram or record of heart sounds with an absolute sphygmogram from the case prepared according to the method of Sahli (Diagnostic Methods, 1911, p. 174). The time interval between the abortive beat and the preceding effective beat when marked off on the absolute sphygmogram would indicate, within the limitations of the method, the diastolic pressure at the instant of the abortive beat.

The line *ab* in Figure 4 may be used according to the directions in Section 2 for constructing the upper end of the diastolic line. Line *cd* was constructed in this way. It will be realized that this corresponds to the results, which if it were possible, should have been obtained by the use of the fifth phase criterion. This accounts for the fact that the line *cd* does not join with the main diastolic line of the figure, which, on account of the water-hammer character of the pulse, it was necessary to obtain by the use of the fourth phase criterion.

The fractional method here described may with propriety be used in many cases other than auricular fibrillation to demonstrate and to measure blood pressure lability; for example, the range of Traube-Hering waves or respiratory waves of blood pressure, of sinus arrhythmia, premature contractions, alternating pulse, etc. Figures 5, 6 and 7 are given as examples.

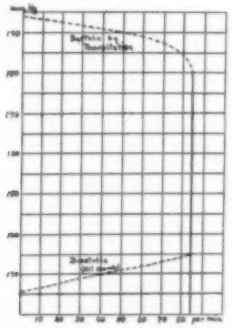

Fig. 5.—Showing a slight amount of pressure lability in an apparently pressure-stable case. Nephritic hypertension.

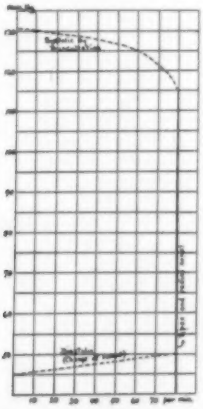

Fig. 6.—Showing a moderate amount of systolic pressure lability due to Cheyne-Stokes respiration. Aortic insufficiency.

Figure 5 is from a case (No. 6220) of nephritic hypertension in which with ordinary examination the pressure seemed stable. The fractional method shows a variation of 5 or 10 mm. Hg in both systolic and diastolic measurements.

Figure 6 is from a case (No. 6397) of aortic insufficiency in which a moderate amount of systolic variation is attributable to Cheyne-

Stokes breathing. (Longer counts may be necessary to obtain smooth curves in cases in which the pressure undulations are as slow as in Cheyne-Stokes breathing.)

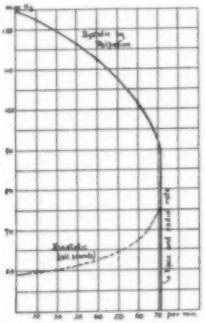

Fig. 7.—Showing much variation of systolic and diastolic pressure due to respiratory arrhythmia.

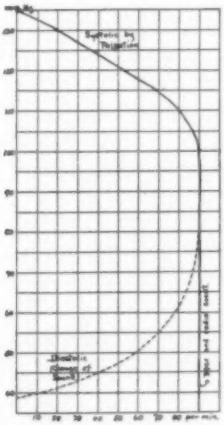

Fig. 8.—Showing a large average pulse pressure as compared with systolic and diastolic pressures in a case of aortic insufficiency with auricular fibrillation.

Figure 7 is from a marked case of respiratory arrhythmia in a boy aged 11 (Case 9680, seen by courtesy of the surgical service). Both systolic and diastolic variability is practically as great as in some of the cases of auricular fibrillation.

DISCUSSION

The Practical Application of Fractional Blood Pressure Determinations. It is the habit of many clinicians to think of blood pressure as a quantity connected with a patient almost as definite and stable as his

body weight, or at least as his temperature. Clinical writers who discuss, for example, changes of 5, 10, 15, or 20 mm. Hg following certain therapeutic procedures, do not as a rule give sufficient weight to the probable latitude of error in the actual determinations or to the many causes of pressure fluctuations over short time intervals. And even when it is realized that in a case of absolute arrhythmia each pulse wave has a different pressure, the inclination is to combine them into a mean or average figure or to take the pressure of the highest beats, and to attach to these figures the same significance that is carried by the measurements in ordinary cases.

It is hoped that the method here described and the figures used for illustration will help to counteract this tendency, and to emphasize first of all the limitations of human blood pressure determinations.[16] Figures 5 and 6 illustrate, respectively, cases of slight and moderate pressure variability in which in the ordinary run of clinical work some one figure for each case would be reported as the blood pressure. From this as well as from observations on the personal factor of observers,[10] it would seem necessary that unusual precautions be taken before reliable inferences can be drawn from small differences in blood pressure.

In the frankly pressure-labile cases further precautions are demanded. Both the amount and the kind (shape of the curve) of pressure variation should be taken into consideration. Average systolic and diastolic pressure can always be calculated from the results of the fractional determinations, after correcting the plotted curves when necessary, as described in Sections 2 and 3. And, with the possible exception of the cases with abortive beats, these averages, based as they are on many observations, may be expected to be as accurate as the usual measurements in normal cases, and probably more so. And in the many instances in which the pressure variation is only moderate and all heart beats produce palpable waves, they undoubtedly bear a fairly close relation to the measurements in pressure-stable cases so far as the usual clinical interpretation of these figures is concerned; i. e., they may be used as indices of hypertension or hypotension, of changes in blood pressure, etc.

The problem is different when many abortive beats are present. If these are included in the calculation, the resulting "average pressure" may have little practical relation to ordinary blood pressure figures. To illustrate: A patient with regular pulse, rate 65 per minute, and systolic pressure 140, is found to have a regularly recurring premature contraction immediately after each effective heart beat, so that

16. I have reviewed the general question of sources of error in blood pressure determinations in the California State Journal of Medicine, 1914, xii, 92.

the heart rate is really 130. The absence of some of the second sounds and the weakness of others belonging to the abortive beats presumably indicates that their systolic pressure is in the neighborhood of the diastolic pressure of the large beats, which is 80 mm. Hg. They cause such small pressure increments, however, that they cannot be felt, and they are negligible so far as the effectiveness of the circulation is concerned. It is obvious that in any consideration of blood flow, vasomotor control, etc., the pressure and the rate of the large beats alone should be taken into account, while the abortive ones would have a separate significance as dissipators of heart energy.

The same is true in cases of premature contractions or auricular fibrillation where the abortive beats are interspersed irregularly. But in these cases there may be every grade of transition between the effective and the abortive beats. The threshold of palpability is a convenient criterion which we have used for distinguishing between the "effective" and the "abortive" groups; and the average pressure of all the beats which can be felt at the wrist may have a somewhat close relationship to the usual measurements in pressure-stable cases. It should be remembered, however, that the distinction at this point is an arbitrary one, and that beats just above the threshold may not have a value for the peripheral circulation proportional to their pressure, while beats just below the threshold may have some value. The highest waves, on the other hand, may not have an efficiency commensurate with their pressure, for the reason that the high pressure is not sustained. Since the ventricle throws out a large volume of blood almost as quickly as a small one,[17] the rapidity of outflow varies according to the volume of the discharge, and with it also the inertia or "hydraulic ram" action of the blood stream. The latter may run up the instantaneous pressure out of all proportion to the efficiency of the wave.[18] That is, the same care should here be taken that is necessary in interpreting ordinary blood pressure readings in such cases as aortic insufficiency.

For the reasons given above, the "average blood pressure" of James and Hart,[7] which includes without distinction the abortive beats, seems to us to be misleading. Certainly for most purposes it is preferable to calculate the average systolic pressure from the palpable beats alone and to give the abortive beats separate consideration.

But if for any cause it is desired to use the general average of both classes of beats, the method of James and Hart would need modification, because it fails to take any account of the pressure of the abortive beats. Since these authors made no use of the method of plotting

17. v. Frey and Krehl: Arch. f. Anat. u. Physiol., 1890, p. 31.
18. Erlanger and Hooker: Johns Hopkins Hosp. Rep., 1904, xii, 145.

results here described, and did not include diastolic pressure in their determinations, the way was not open for them to state approximately the pressure of those beats; and their method of calculating the average amounted to assigning a zero pressure to all the beats which could not be felt at the wrist. This error accounts for the extraordinarily low pressures recorded in some of their cases. The extended "graph" described in Section 3 to represent these beats makes it possible to apply to them the same averaging method as to the waves which can be felt.

The *pulse pressure* so far has not been mentioned. It is clear that its average will be the difference between the average systolic and the average diastolic pressure. Also since waves with highest systolic pressure more often follow the longest pauses (and hence as a rule the lowest diastolic pressures), it is probably true that in cases of auricular fibrillation the greatest pulse pressures are approximately measurable by the difference between the highest systolic pressures and the lowest diastolic. Some light on the variation of pulse pressures below this value might be afforded by a study of the diastolic intervals, but the results would be very problematical, and there appears to be no good way to determine the lower limit of pulse pressure. That the average pulse pressure may have some value is indicated by the results in well marked cases of aortic insufficiency with auricular fibrillation. Figure 8 is from a typical case of this kind. The average pulse pressure is considerably greater than the average diastolic pressure. The usefulness of the average pulse pressure, however, as an index of blood flow, etc., will be limited by the considerations mentioned above in regard to systolic pressure.

SUMMARY

A method is described whereby with the use of the ordinary clinical blood pressure apparatus blood pressure variability may be demonstrated and analyzed. Several types of cardiac arrhythmia are used for illustration. Caution is urged in the interpretation of "average" pressures; especially a distinction should be made between the effective and the abortive beats.

For helpful suggestions I am indebted to Prof. Joseph Erlanger and to my colleague, Dr. James L. Whitney.

CLINICAL STUDIES ON THE RESPIRATION

II. THE ACIDOSIS OF CHRONIC NEPHRITIS *

FRANCIS W. PEABODY, M.D.
BOSTON

Since it has been established that under normal conditions the respiratory center is controlled by the reaction of the blood, and that any increase in blood acidity raises the pulmonary ventilation, the clinical conditions associated with acidosis have assumed a new significance. This is especially true of chronic nephritis, a disease in which dyspnea is not infrequently one of the most disturbing symptoms. Lewis and his associates,[1] and Peabody,[2] have already discussed the association of acidosis and dyspnea in the group of clinical cases which is often classified under the term "cardiorenal disease," but the relation between the two is as yet by no means absolutely clear. In order to get more light on the subject it seemed to be of fundamental importance to obtain rather detailed information as to the mechanism which causes the acidosis, the period at which it begins to develop, the degree to which it attains, and in general the relation which acidosis bears to the clinical course of chronic nephritis.

A considerable body of evidence has already been accumulated to show that acidosis, of a more or less high degree, is apparently a constant accompaniment of uremia. Much, indeed, has been written regarding the possible etiologic relationship between the two conditions. Following the first description of acidosis in uremia by von Jaksch[3] who based his work on the titration of blood, there have been published a large number of observations on the carbon dioxid tension of the alveolar air by Straub and Schlayer;[4] Porges and Leimdorfer,[5] Poulton and Ryffel,[6] and Peabody,[2] as well as more limited series of observations on the hydrogen-ion concentration of the blood by Kreiblich,[7] Rolly[8] and Peabody.[2] The result of all these studies has been,

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Lewis, Ryffel, Wolf, Cotton and Barcroft: Heart, 1913, v, 45; Lewis and Barcroft: Quart. Jour. Med., 1915, viii, 97.
2. Peabody, F. W.: Studies on Acidosis and Dyspnea in Renal and Cardiac Disease, THE ARCHIVES INT. MED., 1914, xiv, 236.
3. Von Jaksch: Ztschr. f. klin. Med., 1888, xiii, 350.
4. Straub and Schlayer: München. med. Wchnschr., 1912, lix, 569.
5. Porges and Leimdorfer: Ztschr. f. klin., Med., 1913, lxxvii, 464.
6. Poulton and Ryffel: Proc. Physiol. Soc., June 28, 1913, Jour. Physiol., 1913, xlvi, 47.
7. Kreiblich: Wien. klin. Wchnschr., 1911, xxiv, 1419.
8. Rolly: München. med. Wchnschr., 1912, lix, 1201.

in general, to show that uremia, at least in its advanced stages, is very frequently, if not always, associated with an acidosis which is sufficiently marked to alter the normal composition of the blood, and to produce a lowering of the carbon dioxid tension. In cases of chronic nephritis without uremia, on the other hand, these investigations of the blood and alveolar air showed little evidence of an acidosis. The whole subject has been approached from a much more fundamental aspect by Sellards,[9] and in a most important series of investigations in which the so-called "alkali tolerance" test was used, he not only describes the acidosis of uremia, but demonstrates beyond doubt the fact that acidosis "is present in an appreciable degree in ordinary grades of nephritis." He shows, furthermore, that the acidosis depends on a retention which is due to imperfect excretion by the kidneys, since the extent of acidosis is roughly parallel to the signs of renal suppression. Palmer[10] has also brought forward evidence of the early interference with the excretion of acids in chronic nephritis.

The question of acidosis may be studied from several points of view. Thus, in ordinary clinical work, the examination of the urine is usually regarded as giving all the information that is necessary. Qualitative tests for abnormal acids, such as the acetone bodies, and determinations of the ammonia excretion are the methods most generally in use. The results of these urinary tests are, however, not infrequently far from satisfactory, for they give information only as to the amount of acid that is being excreted by the organism, and leave one wholly in the dark as to the actual conditions existing in the blood and tissues. That the examination of the urine shall have any great diagnostic significance presupposes the fact that the increased acids are being excreted, while it is the failure to excrete acids—whether formed in normal or abnormal amounts—that forms the danger of acidosis. In chronic nephritis, in which interference with the renal function is the most essential element, the usual methods of studying the urine would, of course, be wholly unreliable for giving an index of the formation or retention of acids in the body. Much more significant information can be obtained from the blood. In spite of the large amount of acid that passes into the blood as a result of the ingestion of food and of the processes of metabolism, the normal reaction of the blood remains constant. This preservation of its normal reaction is upheld by the excretion of acids through lungs and kidneys, as well as by the chemical composition of the blood. The latter is peculiarly well adapted to the taking up of a maximum of acid with a minimum change of reaction. When, however, there is a great

9. Sellards: Bull. John's Hopkins Hosp., 1912, xxiii, 289; ibid., 1914, xxv, 141.
10. Palmer: Med. Communicat., Massachusetts Med. Soc., 1913, xxiv, 133.

abnormal increase in the formation of acids, or when the acids are not properly excreted by the kidneys, so that large amounts accumulate in the blood, the blood will necessarily become more acid in reaction. Such a rise in acidity will stimulate the respiration, the carbon dioxid tension of the blood will be reduced and the normal reaction of the blood will be maintained. Thus a diminution of the carbon dioxid tension of the blood, or, what is the same thing, a diminution of the carbon dioxid tension of the alveolar air, will be an index of the increase of the nonvolatile acids in the blood. Such an index will be of infinitely greater value as a guide to the condition within the body at any given time than can be obtained from the urine, and is of primary significance when one is considering the subject from the point of view of the control of respiration. Of more fundamental importance would be a means of studying acidosis in the cells or tissues, for it is the preservation of the normal reaction of the cells that is really essential to the organism. Enzyme activities, and in all probability the majority of metabolic processes, proceed best at certain definite reactions, and many can only take place within certain narrow limits of reaction. Unfortunately, methods have not yet been devised which allow us to gain much insight into the obscure field of cellular metabolism, and the problem of tissue acidosis can only be approached indirectly. Probably the most delicate index of acidosis is obtained by the use of the so-called "alkali tolerance" test, first described and studied by Sellards,[9] but simultaneously worked out by Palmer.[10] In a normal individual the ingestion of 5, or at most 10 grams of sodium bicarbonate suffices to change the reaction of the urine from acid to alkaline, but if there is any acidosis, either from excessive formation or from simple retention of acid, a much larger amount of alkali is required. It seems probable that during the gradual development of an acidosis the organism draws on the reserve supply of base in the tissues to neutralize the acids, and when, subsequently, an excess of base is provided, as by giving sodium bicarbonate, it is used to replenish the exhausted stores in the tissue before it is allowed to pass out in the urine. A comparison of various methods for detecting acidosis shows that the amount of sodium bicarbonate which is needed to change the reaction of the urine is a delicate index of the extent of the acidosis. Moreover, in spite of its simplicity, it gives perhaps the earliest evidence of the development of an acidosis, for it apparently tells when even a small inroad on the reserve supply of bases in the tissues has been made. The "alkali tolerance" test may thus be quite safely considered as a general, rough guide to the degree of acidosis in the tissues. Only at a later period, when a considerable amount of acid has been accumulated in the tissues and in the blood,

does the composition of the blood change so that the alveolar carbon dioxid tension begins to fall. It is of course this latter point—the time at which a shift in hydrogen ion concentration of the blood stimulates the respiratory center and causes an increase of pulmonary ventilation with a consequent lowering of alveolar carbon dioxid tension, that is of special significance from the point of view of studies of the respiration.

In the series of cases of chronic nephritis reported on in the present paper an attempt has been made to correlate what may be considered as two stages in the development of the acidosis, with the course of the disease as indicated by renal function tests. The "alkali tolerance" test has been applied to find the earliest indication of acidosis, and the carbon dioxid tension of the alveolar air has been determined to show when the acidosis has begun to affect the balance between volatile and nonvolatile acids in the blood. The usual method for the "alkali tolerance" test has been to give 5 grams of sodium bicarbonate by mouth every two hours until the urine becomes alkaline to litmus paper. This rather rough method has given results that are in general wholly satisfactory. The high normal limit is taken as 10 grams of sodium bicarbonate. In most normal persons the urine becomes alkaline after 5 grams. The carbon dioxid tension of the alveolar air was determined by the Plesch-Higgins[11] method, which has been extensively used in this laboratory, and has proved itself most satisfactory for clinical work. As an indication of the severity of the nephritis the functional capacity of the kidneys was studied by the phenolsulphonephthalein test, and in some instances, by the determination of nitrogen retention. Dr. J. P. O'Hare has been kind enough to give me his figures for the total nonprotein nitrogen, or for the urea nitrogen of the blood in the cases which were studied by him in another connection.

Since cardiac insufficiency may of itself cause an acidosis, it is of importance from the present point of view that the cases of nephritis to be studied should be as free as possible from any involvement of the heart. Ideal cases are, of course, very difficult to find, as so large a proportion of all cases of chronic nephritis are associated with cardiac hypertrophy, and, in the later stages at least, with evidences of cardiac weakness. By careful selection, however, a group of cases has been accumulated in which the cardiac element could be fairly safely ruled out. Many gave in their histories symptoms suggesting myocardial weakness, such as dyspnea on exertion, and others had passed through periods of more or less definite cardiac decompensation, but when they were investigated for the present purpose the cir-

11. Boothby, Walter M., and Peabody, F. W.: A Comparison of Methods of Obtaining Alveolar Air, THE ARCHIVES INT. MED., 1914, xiii, 497.

culatory element was absent, or, in a few instances, wholly secondary in importance.

The cases fall naturally into three groups. The first (Table 1) consists of patients in whom there was evidence of a definite, but not particularly severe nephritis. The diagnosis was based on the urinary findings and usually on an associated hypertension and cardiac hypertrophy. In all of these cases the phenolsulphonephthalein output, and the determinations of blood urea, with one exception, indicate that the action of the kidneys was functionally sufficient. The alkali tolerance test was normal in every case in which it was tried, and the carbon dioxid content of the alveolar air was found to be normal. Thus, in this series of patients with comparatively mild chronic nephritis, no evidence of acidosis was found.

TABLE 1.—Cases Showing Normal Phthalein Output and Normal Alveolar Carbon Dioxid Tension

Case No.	Hospital No.	Blood Pressure mm. Hg.	Phthalein Output in Two Hrs. Per Cent.	Urea Nitrogen in Blood mg.	Alkali Tolerance Gm. $NaHCO_3$	Alveolar Carbon Dioxid Tension mm.
1	2552	110	58	....	10	50.3
2	2324	90	52	9.25	10	42.3
3	2548	140	65	9.4	10	43.5
4	M'D.	178	63	....	10	49.9
5	2077	210	50	22.5	10	43.4
6	17319	220	55	....	5	....
7	428	195	70	....	..	44.1
8	2081	160	52	....	..	40.0 *
9	426	100	55	....	..	42.7
10	2237	160	60	12.3	10	....

* Cardiorenal compensated.

Table 2 consists of a group of rather more severe cases. The phenolsulphonephthalein test and the nitrogen retention determinations show that in all of them the functional capacity of the kidneys was below normal. The degree to which renal efficiency was impaired varied considerably, being slight in some instances, but great in others. The alevolar carbon dioxid determinations were always normal, indicating that there was no great accumulation of nonvolatile acid in the blood. "Alkali tolerance" tests were done in only five cases, but in all of these there was an increase above normal in the amount of sodium bicarbonate required to make the urine alkaline in reaction. One patient became nauseated after taking 50 grams, and it was not possible to complete the test. It is worth noting that the increase in "alkali tolerance" runs exactly parallel to the decrease in phenolsul-

phonephthalein elimination. Thus in this group of patients with chronic nephritis of higher grade, and with kidneys which are more or less inefficient functionally, the "alkali tolerance" test shows that there may be a loss of base to the body, an early stage in the develop-

TABLE 2.—Cases Showing Low Phthalein Output and Normal Alveolar Carbon Dioxid Tension

Case No.	Hospital No.	Blood Pressure mm. Hg.	Phthalein Output in Two Hrs. Per Cent.	Nonprot. Nitrogen in Blood mg.	Alkali Tolerance Gm. $NaHCO_3$	Alveolar Carbon Dioxid Tension mm.
1	2611	195	23	25 *	25	43.6
2	2429	160	39	18.75 *	15	40.3
3	2124	250	36	33.13 *	..	45.1
4	621	280	Traces	90	..	40.3
5	2111	180	10	55.5	50 +	42.8
6	477	200	35	....	..	41.4
7	2202	245	18	71.9	..	41.9
8	762	192	25	50.0	..	40.2
9	590	145	29	....	..	42.7
10	2762	260	28	32.5 *	35	41.6
11	655	230	0	279.0	..	41.3
12	2739	200	12	42.7 *	20	41.4

* Urea nitrogen.

TABLE 3.—Cases Showing Low Phthalein Output and Low Carbon Dioxid Tension

Case No.	Hospital No.	Blood Pressure mm. Hg.	Phthalein Output in Two Hrs. Per Cent.	Nonprot. Nitrogen in Blood mg.	Alkali Tolerance Gm. $NaHCO_3$	Alveolar Carbon Dioxid Tension mm.
1	2564	240	Trace	101.5 *	80	31.1
2	2567	195	Trace	57.5 *	55	35.8
3	2006	200	Trace	90.9	50 +	19.1
4	2111	180	6	55.6 *+	50 +	35.8
5	673	205	0	200.0	..	33.8
6	2108	160	15	55.5	80	33.7
7	573	230	0	90.5	..	31.7
8	132	170	0	....	..	6.0
9	2730	168	27	48.0 *	50	35.3

* Urea nitrogen.

ment of acidosis, but the alveolar air determinations are normal and do not suggest that the nonvolatile acids are increased in the blood.

The nine patients in the third group (Table 3) had very advanced chronic nephritis. Six of them died within a few days or weeks of

the time when these observations were made, and the three who were discharged from hospital were given a bad prognosis. The phenolsulphonephthalein test, and the nitrogen retention figures both indicate that the functional efficiency of the kidneys was extremely low. Even in the two instances showing an output of 27 and 15 per cent. of phenolsulphonephthalein, the high values for the nonprotein nitrogen and for the urea nitrogen in the blood are evidence of severe nephritis. "Alkali tolerance" tests in six cases show a marked acidosis, the figures being on the whole considerably higher than in the previous group of less severe cases. The alveolar carbon dioxid tension was below normal in every case, and in two instances reached extremely low values. There is, however, no strict parallelism between the clinical condition and the fall in carbon dioxid tension, for while the lowest figures occurred during the days just before death, a tension of 33.8 mm. was found in one patient who died in uremia within twenty-four hours. In most of these cases the carbon dioxid tension has been low when the patient entered the hospital, but occasionally it has been possible to follow the development of the acidosis in its relation to the course of the disease. Thus in Case 2111 the patient was in fairly good condition when he came into the hospital. The phenolsulphonephthalein output was 10 per cent. in two hours, the nonprotein nitrogen in the blood 55.5 mg., and the alveolar carbon dioxid tension was 42.8 mm. Two weeks later his "alkali tolerance" was tested and found to be 50 grams +. One month after admission the clinical picture had changed and the patient was going down hill rapidly. The phenolsulphonephthalein output was 6 per cent. and the alveolar carbon dioxid tension was only 35.8 mm. In two days more it had dropped to 33.4 mm., and in five days he died. In this group of patients, then, with very advanced chronic nephritis, and with kidneys whose functional capacity is greatly reduced, there is evidence of a marked acidosis, involving not only a loss of base from the tissues, but the accumulation of considerable amounts of nonvolatile acid in the blood.

The facts which have been brought out here all bear out the theory that the acidosis of renal disease is due to retention. This is in accordance with the views held by Sellards[12] and with the opinions of Porges and Leimdorfer[13] regarding the cause of the acidosis of uremia. Apparently, so long as the functional capacity of the kidney is unimpaired, or is so slightly decreased that there is no demonstrable retention of phenolsulphonephthalein or of nonprotein nitrogen, there are no signs of acidosis. As soon as there begins to be any retention, it

12. Sellards: Bull. Johns Hopkins Hosp., 1914, xxv, 141.
13. Porges and Leimdorfer: Ztschr. f. klin. Med., 1913, lxxvii, 464.

is frequently found that an acidosis is developing. Sellards[14] says that "in all cases in which the tolerance to bicarbonate is markedly increased, the phenolsulphonephthalein output is very low. On the other hand the excretion of bicarbonate is practically normal in some of these cases in which the phenolsulphonephthalein test shows a functional insufficiency."

An interference with the excretion of acids runs roughly parallel to the interference with the excretion of phenolsulphonephthalein, and the retained acids draw on the reserve supply of base in the body. These reserves suffice to protect the body from the development of a serious grade of acidosis for a long time, for it is only when excretion is very markedly limited that this protective mechanism fails and acids begin to accumulate in the blood. If large amounts of base are supplied to the body, even after a severe acidosis has developed, the alveolar carbon dioxid will rise, and conditions will become normal again. It may then be quite a long time before this new reserve is used up and before the carbon dioxid tension begins to fall again. The situation is very different in severe diabetic acidosis in which abnormally large amounts of acids are being formed, and correspondingly large amounts of base are required. In chronic nephritis the formation of acids is probably not increased, but the body gradually goes into bankruptcy, as they are not excreted, and the organism loses the advantage of the mechanism by which the kidney excretes acid and retains base for further use. There is, of course, the possibility that the amount of acid substances formed in chronic nephritis is somewhat more than the normal. Mosenthal's work[15] showing a specific increase of protein metabolism, bears on this subject. This, however, would not be a large factor, and in general, the acidosis of chronic nephritis may be considered as being due to the retention of the normal acid products of metabolism.

Having shown that during the later stages of chronic nephritis a sufficient grade of acidosis may develop to cause a depression of the carbon dioxid tension of the alveolar air, it is now of importance to consider in more detail how great the acidosis actually is, and what relation it bears to uremia. In most cases the acidosis does not seem to be particularly great. The alveolar carbon dioxid tension usually runs from 25 to 35 mm. during the days in which uremia is developing and even after coma has set in. The significance of these figures may perhaps be best understood by comparing them with the results found

14. Sellards: Bull. Johns Hopkins Hosp., 1912, xxiii, 289.

15. Mosenthal, H. O.: Nitrogen Metabolism and the Significance of the Non-Protein Nitrogen of the Blood in Experimental Uranium Nephritis, THE ARCHIVES INT. MED., 1914, xiv, 844.

in diabetes, in which it has been quite definitely established that while a tension of 30 to 20 mm. indicates a serious acidosis, the condition is usually not critical until it drops below 20 mm. During diabetic coma the carbon dioxid tension is apt to be about 10 mm. or less. This comparison of the alveolar air in diabetes with that in nephritis suggests, of course, that in many cases of uremia acidosis plays a very subordinate part. There is, however, a well-defined group of cases of advanced chronic nephritis in which the whole clinical picture simulates closely that of diabetic acidosis. These patients are at first somnolent, and then pass into a deep sleep or coma. The respiration becomes deeper, and when the case is fully developed, there is typical "air hunger." Acetone and diacetic acid are present in only small amounts in the urine, or they may be absent. In this group of cases the onset of severe, terminal, uremic symptoms is associated with a fall of the carbon dioxid tension to values as low as are found in diabetic coma. In one instance the tension was 4.59 mm. during coma. Another was of unusual interest in the response shown to alkali therapy. The patient was a woman, 45 years old, with a history of nephritis extending over several years. Her blood pressure was about 200 mm. and the nonprotein nitrogen in her blood had risen to 90 mg. per 100 c.c. of blood. For over a month the phenolsulphonephthalein test had shown practically no elimination of the dye in her urine. Her general condition, however, remained rather remarkably good, and except for headaches there was no evidence of uremia until January 11. On this day she first began to complain of being short of breath. The alveolar carbon dioxid tension was 19.1 mm. Two days later, on January 13, she was unconscious and her respiration was slow but so deep as to be quite typical of "air hunger." The alveolar air was not taken at this time, but 300 c.c. of 4.7 per cent. sodium bicarbonate solution were given intravenously. On the following morning the carbon dioxid tension was 23.4 mm. This indicated a marked acidosis, and as the "air hunger" persisted, a further intravenous injection of 700 c.c. was given later in the day. On the following morning the clinical picture had entirely changed. The patient was conscious and recognized every one, but she was greatly nauseated and still looked very sick. The "air hunger" had disappeared and the respiration was of the shallow, slow, and irregular type with rather prolonged periods of apnea such as is commonly seen in advanced nephritis. The alveolar carbon dioxid tension had risen to the normal value of 41.5 mm. On the next morning it had fallen to 36.9 mm. Respiration was slightly deeper, with occasional sighing respirations, but it did not suggest "air hunger." She was conscious and responded fairly well to questions but was very dull. An attempt was

made to ward off the further development of acidosis by giving 375 c.c. of 5 per cent. sodium bicarbonate intravenously, but it was unsuccessful, for on the next day the alveolar carbon dioxid tension had dropped to 25.1 mm., her respiration was deeper and more rapid, and she was becoming unconscious. On January 17 she was comatose, and had begun to have convulsions. Another intravenous alkali injection was without effect and the patient died January 18. Sellards has described similar cases of uremia in which "air hunger" was a prominent symptom, and indeed the clinical picture is one that is generally recognized.

The investigations described here agree well with those of other observers, and make the relation between acidosis and uremia quite clear. It seems certain that some degree of acidosis is present in all cases of uremia. Usually it is marked enough to cause a lowering of the alveolar carbon dioxid tension, but often it is not of high enough grade to be of itself an important element in the symptomatology of the case. In a limited number of cases the onset of severe uremia is associated with the development of an acidosis which is extensive enough to produce coma and "air hunger" and which may dominate the clinical picture.

The therapeutic results obtained by the administration of alkali in uremia confirm this point of view. In the case just described the sodium bicarbonate was undoubtedly beneficial in its action, for it relieved dyspnea and restored consciousness. The improvement was only temporary, however, for acidosis is certainly only one factor in uremia, and the patient was necessarily doomed to succumb to the other results of renal suppression. Similar and even better results are reported by Sellards after the administration of alkali in this type of case. The evidence is thus good that in the group of uremic patients with signs of marked acidosis, alkali therapy is indicated, and may produce great temporary improvement. In the group of cases in which the acidosis only produces a slight fall in the alveolar carbon dioxid tension, and in which there are no symptoms directly due to the acidosis, the results obtained by giving alkali are much more questionable. The fact that the body has lost part of its reserve supply of base, and that it is on the edge of a severe acidosis makes the administration of alkali a logical indication. The effect is hard to determine, as there are so few definite symptoms to go by.

The respiration in advanced cases of chronic nephritis is not typical of acidosis even when there is a slight depression of the carbon dioxid tension. As in diabetes, the evidences of "air hunger" usually begin to appear only when the carbon dioxid tension drops below 20 or at most 25 mm. Most cases of advanced nephritis have an irregular, shallow,

periodic type of respiration, with a tendency to the development of Cheyne-Stokes respiration particularly when they begin to sleep. The irregularity or periodicity of the breathing is frequently not very evident on casual examination, but it comes out as soon as pneumographic tracings are taken. At night, with the general depression of nervous excitability, the periodicity becomes more marked, and in many instances the distressing attacks of nocturnal dyspnea are due to Cheyne-Stokes respiration. Even when the periods of apnea and dyspnea are not definitely demarcated, a pneumographic tracing may show that a period of very shallow breathing, followed by a short interval of apnea, precedes the dyspneic attack which arouses the patient from his sleep to severe physical and mental distress. This periodic type of respiration is not a result of acidosis, for, in a number of cases, pneumographic records have shown that it exists after enough alkali has been given to bring the alveolar air back to its normal value, in exactly the same way that it did before the acidosis was overcome. It was also interesting to notice in the case of nephritis with acidosis described above, that when enough alkali had been given to raise the carbon dioxid tension and overcome the "air hunger," the respiration became shallow and irregular, just as it is in most advanced cases of chronic nephritis. It was thus possible to separate the type of respiration characteristic of nephritis itself from that which depended on the acidosis occurring during the nephritis. On the other hand, some patients with milder acidosis seem to be distinctly more comfortable and to have much better nights after they have received alkali. Inasmuch as patients with acidosis are rendered dyspneic more easily than are normal persons by the inspiration of carbon dioxid,[16] and are thus apparently peculiarly susceptible to dyspnea, it would seem wholly likely that overcoming the acidosis in patients with advanced nephritis might increase their comfort by diminishing the tendency to dyspnea.

When chronic nephritis is associated with cardiac weakness the question of acidosis becomes much more complicated, as a new element is added. There is not only the acidosis of nephritis, due to inefficient renal excretion, but there may also be an accumulation of acid metabolic products which are the result of an inadequacy of the supply of oxygen reaching the tissues. Such patients may show a lowering of the alveolar carbon dioxid tension when they are first seen, and while their hearts are more or less decompensated,. If, however, the kidneys are not too badly involved, the acidosis will disappear shortly. As the circulation becomes compensated, the production of acids due to circulatory insufficiency will cease, oxidations will go on normally, and the kidneys will excrete the accumulated acids. Since the reserve supply

16. Peabody: THE ARCHIVES INT. MED., this issue, p. 955.

of base may be decreased in patients with chronic nephritis, so that they are constantly nearer than normal to the development of an acidosis, it is quite probable that a degree of cardiac insufficiency which will produce dyspnea in them would not affect a person who could neutralize and excrete acids normally.

CONCLUSIONS

In mild cases of uncomplicated chronic nephritis, in which the phenolsulphonephthalein test shows a normal renal function, there is usually little or no acidosis.

More advanced cases, showing moderate or even extreme decrease in the phenolsulphonephthalein output, show an acidosis by the "alkali tolerance" test, but there may be no fall in the alveolar carbon dioxid tension.

Only in very advanced cases is the acidosis usually so marked as to cause a decrease in the alveolar carbon dioxid tension. Most cases in which the alveolar carbon dioxid tension is below normal show a phenolsulphonephthalein output which is below 10 per cent. in two hours. On the other hand cases showing a phenolsulphonephthalein output of "traces" or less may have a normal alveolar carbon dioxid tension.

The acidosis of chronic nephritis is due to a retention, resulting from inefficient renal excretion.

Acidosis is probably a very constant feature of uremia, but only in a limited number of cases is it of sufficient grade to cause definite clinical symptoms analogous to those seen in advanced diabetes. In these cases the symptoms caused by the acidosis may be relieved by alkali therapy.

THE ACTION OF THE VAGI ON THE HEART IN PAROXYSMAL TACHYCARDIA *

G. CANBY ROBINSON, M.D.
ST. LOUIS

The influence of the vagi on the heart in paroxysmal tachycardia is of interest because of the possible causative rôle derangements of the nervous mechanism controlling heart rate may play in the disease, and because vagus stimulation may in some cases bring about a cessation of the tachycardia. I wish to consider this influence from a somewhat different point of view, as it seems possible to draw certain inferences concerning the mode of action of the vagi, by comparing cases in which vagus stimulation by pressure is effectual in stopping the tachycardia with those in which it is ineffectual.

Cohn and Fraser[1] have reported two cases of paroxysmal tachycardia which could be stopped by pressure over the vagi, one case apparently of auricular origin in which the right vagus was especially effectual, and the other apparently of ventricular origin in which the left vagus was more effectual than the right. There have been numerous reports of such cases in the literature.

Much less has been written, however, concerning cases in which pressure over the vagi failed to affect the very rapid heart rate, and this failure has apparently not been discussed. I wish to report observations on two cases of paroxysmal tachycardia in which the rapid heart rate could not be influenced by vagus pressure, and to draw some inferences regarding vagus action from a comparison of these two groups of cases.

CASE 1.—A young man of 26 walked into the dispensary complaining of heart trouble, which he said came on suddenly. He had been having such attacks for the past five years, lasting from a few minutes to thirty-six hours. There was no previous illness that could be considered as an etiologic factor of a cardiac disorder. His heart was beating at the rate of 204 per minute.

Electrocardiograms were made immediately and numerous attempts were made to affect the heart rate by pressure over one or the other vagus. Electrocardiograms during the paroxysms were not of unusual form (Fig. 1).

Pressure over the right vagus was always entirely without effect, the records made during the pressure showing no alteration in rate, form or in relation of auricles to ventricles. On several occasions, however, the left vagus caused cessation of the rapid rate momentarily, but it was resumed, even while pres-

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* From the Department of Internal Medicine, Washington University Medical School.

1. Cohn and Fraser: Heart, 1914, v, 93.

sure on the vagus was being maintained (Fig. 2). The electrocardiograms obtained during the left vagus pressure showed that, according to the interpretation of the curves, there was a marked lengthening of conduction from auricles to ventricles and finally a block, followed by stoppage of the auricles. The rapid rate was resumed at first by contractions of ventricular origin or by ventricular asynchronism following auricular contractions. The action of the left vagus, when effectual, was quite constant (Fig. 3). The paroxysm ceased suddenly about ten hours later, when the patient was in the hospital, and electrocardiograms of the normal, slow rate were obtained (Fig. 4). They do not differ materially, when the change of rate and consequent spreading out of the various waves is considered, from those obtained during the tachycardia.

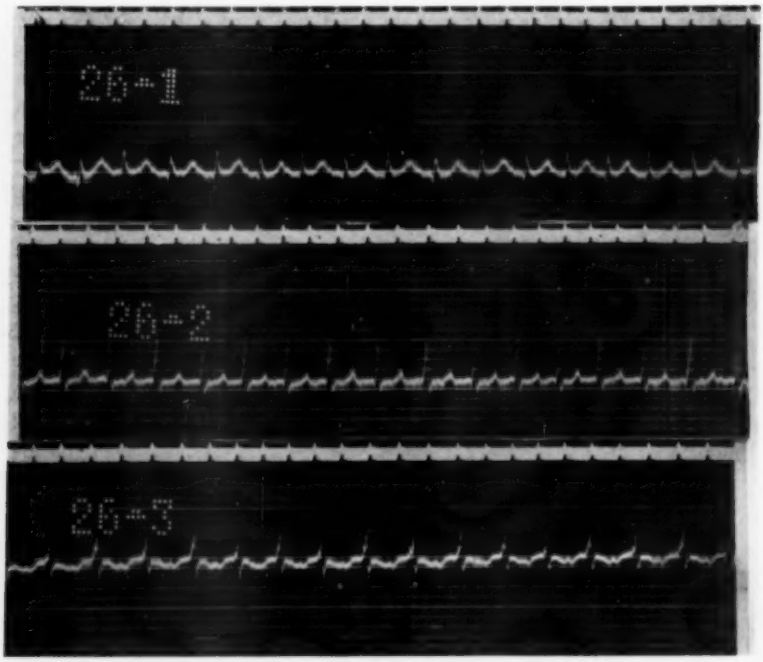

Fig. 1 (Case 1).—Record obtained during an attack of tachycardia.

During the normal slow rate, vagus pressure over either nerve was definitely effectual in slowing the heart, the right being more effectual than the left. When 1/50 grain of atropin was administered hypodermically, the heart rate as recorded by electrocardiograms showed an increase of twenty-seven beats per minute as is shown by the accompanying chart (Fig. 5). The patient left the hospital, having had no further attacks of tachycardia while under observation, but has had frequent attacks during the past year, as reported by his physician.

Case 2.—A woman of 39 who had had rheumatism at the age of 10 and again at 27, gave a history of attacks of cardiac palpitation and rapid heart action beginning at the age of 15. These attacks have been more frequent

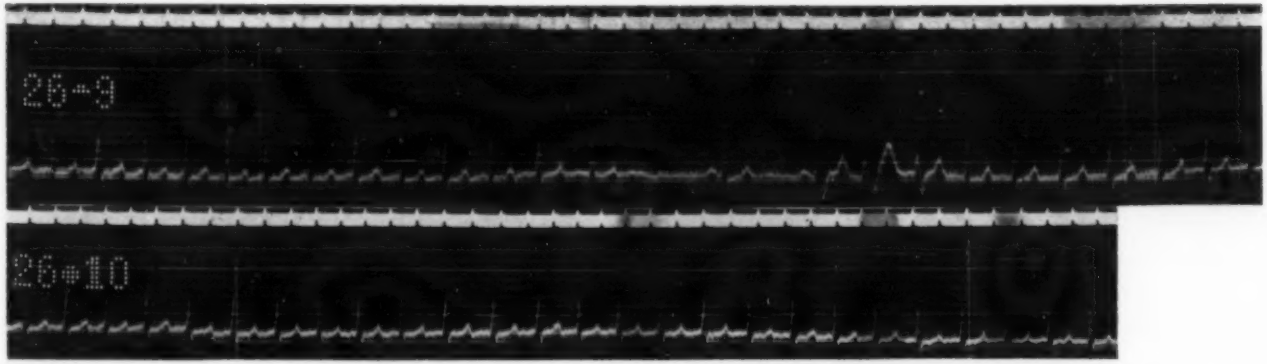

Fig. 2 (Case 1).—Record obtained while pressure over each vagus was being exerted. Momentary effect of left vagus pressure and absence of effect of right vagus pressure are seen.

Fig. 3 (Case 1).—Record obtained during left vagus pressure, showing the constancy in the response to pressure over this nerve.

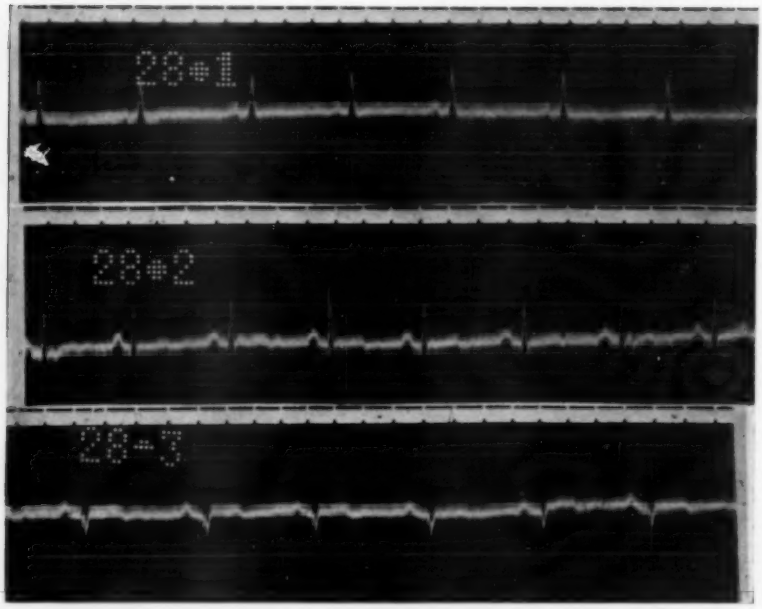

Fig. 4 (Case 1).—Record obtained after the heart had resumed its normal rate.

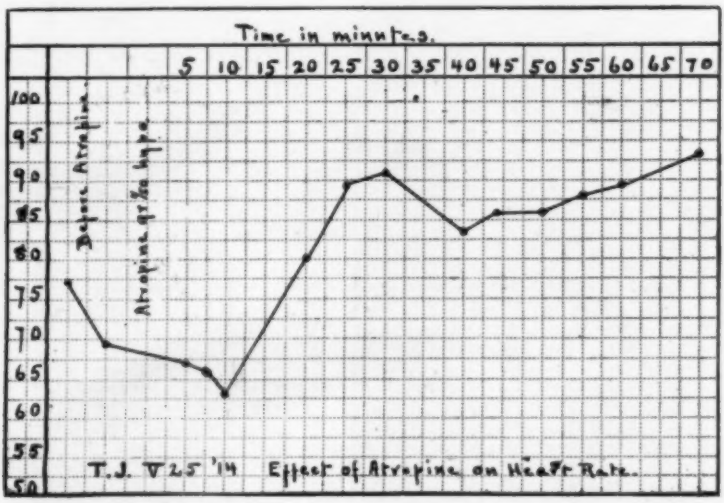

Fig. 5 (Case 1).—Chart showing the increase in the heart rate following the administration of atropin.

during the past year, but have not materially interfered with her duties as trained nurse doing institutional work. The attacks begin and end suddenly, and last from about one hour to three days. They can be stopped at times by vomiting and the patient sometimes takes an emetic to produce this result. She has aortic and mitral regurgitation. During her stay of several weeks in the hospital she had one attack lasting about two hours, when her heart rate was 220. Electrocardiograms were obtained during this attack (Fig. 6). During this attack pressure on each vagus was made several times and the records

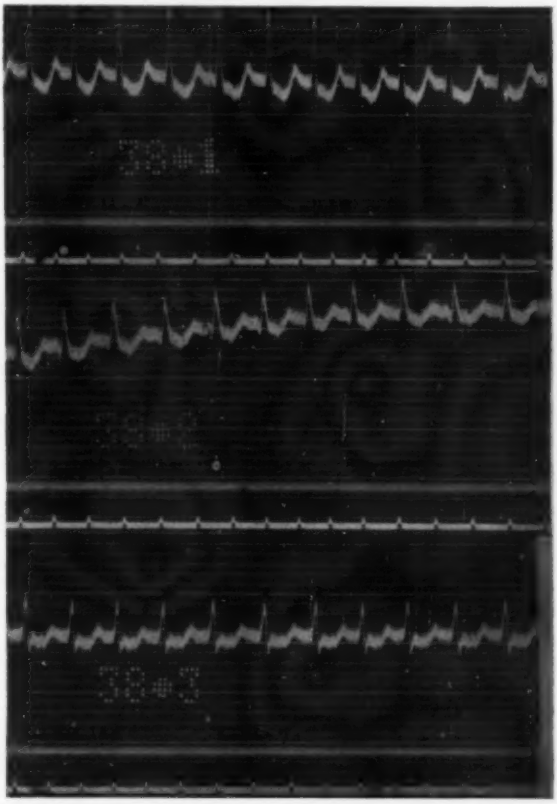

Fig. 6 (Case 2).—Record obtained during an attack of tachycardia.

made during this procedure showed that the rate and cardiac mechanism were entirely unaffected. The tachycardia ceased spontaneously.

The curves obtained during the time of normal slow cardiac activity showed a definite change in form of the complexes (Fig. 7) with a very distinct splitting of the P wave in the second lead, and the frequent occurrence of premature ectopic auricular contractions. Pressure over each vagus was effectual in causing a slight slowing of the cardiac rate and the hypodermic injection of 1/30 grain of atropin caused an acceleration of about thirty beats per minute, as is shown in the chart (Fig. 8). It did not produce tachycardia.

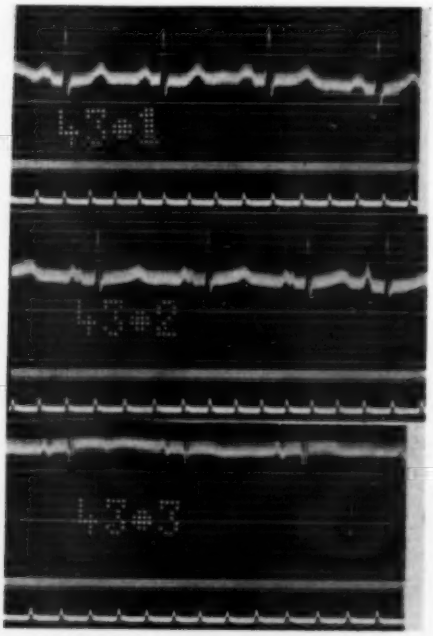

Fig. 7 (Case 2).—Record obtained after the heart had resumed its normal rate.

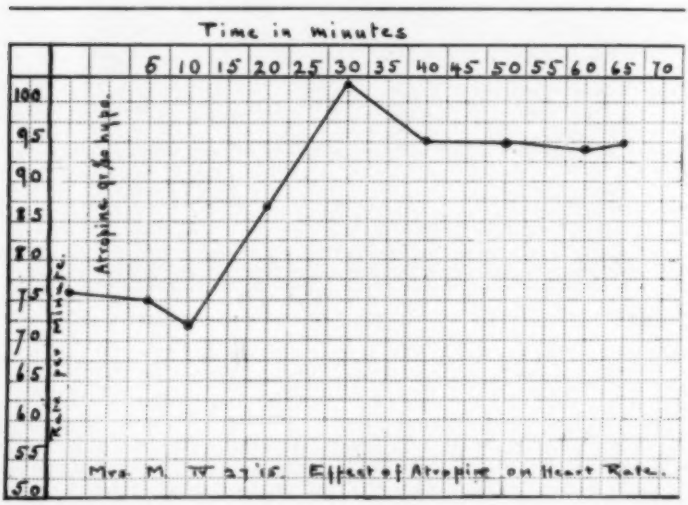

Fig. 8 (Case 2).—Chart showing the effect of atropin on heart rate.

These two cases of paroxysmal tachycardia are representative of those in which vagus pressure fails to abolish the tachycardia. The cause of the ineffectiveness is not, however, any permanent derangement of the cardiovagal inhibitory mechanism, as in both cases the heart rate was slowed by vagus pressure and increased by vagus paralysis with atropin. Why is it then that stimulation of the vagi by pressure is effectual in some cases and not in others? It seems probable that this difference depends on the character of the cardiac derangement responsible for the tachycardia. It is generally held that true paroxysmal tachycardia usually depends on rapid stimulus

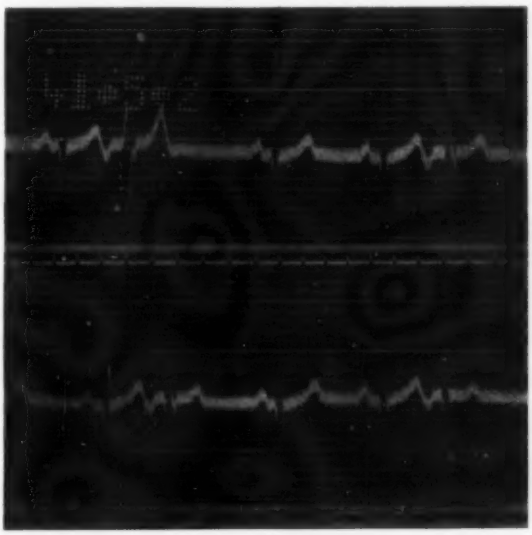

Fig. 9.—Record showing variations in the form of the ventricular complexes which may follow ectopic auricular contractions.

formation in a point outside of the site of the normal cardiac pacemaker, and that it consists of rapidly recurring ectopic beats. These ectopic beats usually arise in a given case in the same part of the cardiac structure. It seems probable that the influence which the vagi will have in controlling these ectopic beats depends on the anatomical relation between the distribution of the vagi and the point taking up the rôle of hyperactive pace-maker. In some cases this point may lie in a part of the heart to which the right vagus is especially distributed, as in Cohn and Fraser's first case; in others, this point may lie in a zone to which the left vagus is more completely distributed, as

in their second case. Other cases may owe their tachycardia to a point of origin to which one nerve only is distributed, but so meagerly as to have slight control over it, as in our first case, while the seat of origin in others may lie in a point of the heart to which the vagus has no distribution and therefore cannot influence it, as in our second case. These cases are brought forward as further evidence for the idea that the influence of each vagus on the heart depends on its anatomical distribution, as has been already suggested,[2] in accounting for the differences in the effects of the right and left vagi.

It is not permissible, however, to use these cases as evidence of the exact distribution of the vagi, as it seems impossible to locate the point of origin of the abnormal stimuli from the form of the electrocardiographic curves. Curves obtained from a case with ectopic premature auricular contractions, have shown that these abnormal contractions, although suprajunctional in origin, as attested by a conduction time of normal or slightly prolonged length, may give rise to ventricular complexes of various and abnormal forms (Fig. 9). In paroxysmal tachycardia, when the ventricular complex is quite similar to that obtained when the heart is beating at a normal slow rate, the point of origin is surely not in the ventricles, but an abnormal form of ventricular complex obtained during the tachycardia should not, in the light of the curve shown in Figure 9, be considered as conclusive evidence of a ventricular origin of the tachycardia.

These cases of tachycardia may be taken, therefore, only as evidence that the influence of the vagi differs in degree on different parts of the heart, and that this difference probably depends on their anatomical distribution.

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2. Robinson and Draper: Jour. Exper. Med., 1912, xv, 14.

THE CARBOHYDRATE METABOLISM IN HYPERTHYROIDISM AS DETERMINED BY EXAMINATION OF BLOOD AND URINE*

H. RAWLE GEYELIN, M.D.
NEW YORK

A lowered tolerance to carbohydrate, as shown by alimentary and spontaneous glucosuria, has long been a well-recognized symptom of hyperthyroidism, and by many authors regarded as a most important one. Scarcely any two observers agree, however, as to the frequency of its occurrence, and many hypotheses have been advanced to explain its presence in some cases and absence in others.

It was thought that a systematic study of the sugar in the blood concomitantly with that of the urine under uniform conditions might throw some light on this subject, and give us a more accurate knowledge of the frequency and degree of lowered carbohydrate tolerance in this disease. For this reason the present work was undertaken. While it was in progress, Flesch[1] reported a series of forty cases of hyperthyroidism with special reference to the concentration of sugar in the blood under various conditions. His results, which are at variance with mine, are here briefly outlined.

1. No case showed spontaneous hyperglycemia. Only nine cases, six before and three after operation, however, were studied fasting, and of these, one before operation gave a blood-sugar reading of 0.102 per cent., and one of the three examined after operation showed 0.110 per cent.

2. Sixty per cent. of the cases showed an "alimentary hyperglycemia," blood being taken one hour after 100 gm. of glucose.

In view of what is to follow, it seems desirable to point out that Flesch worked with the old Knapp method as used by Tachau, with 15 c.c. of blood. This method is little used now, because of its unwieldiness and lengthy technic.

Flesch did not examine the urine for sugar in any of his cases.

Tachau[2] found an alimentary hyperglycemia in a few cases of hyperthyroidism, and failed to find it in others.

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* From the Blumenthal Fellowship Foundation of the Medical Clinic, Presbyterian Hospital, Columbia University.

1. Flesch, Max: Beitr. z. klin. Chir. (Bruns'), 1912, p. 236.
2. Tachau: Deutsch. Arch. f. klin. Med., 1911, civ, 445.

These observations, outside of a few isolated cases, reported by other observers, are the only ones to date. All lack uniformity in method of estimating blood sugar, condition of patient at time of taking blood, as regards diet, fever, etc., and in their failure to compare normal controls with the cases studied.

A review of the literature on glucosuria in hyperthyroidism is to be found in Rosenberger,[3] Allen[4] or Magnus-Levy,[5] and Schulze.[6]

Its frequency, either spontaneous or alimentary, is, as I have said, much disputed, the highest figures giving 69 per cent. and the lowest less than 1 per cent. Garrod, in his Lettsonian Lectures,[7] sums up as follows: "Undoubtedly in many cases no diminution of tolerance can be detected, but my own experience leads me to take my stand with those who hold that it is by no means an uncommon phenomenon. In not a few cases, spontaneous excretion of sugar, of a transitory or intermittent kind, is observed, if carefully watched for, and in others, as I have already mentioned, persistent glucosuria with the usual attendant symptoms which go to make up the picture of diabetes." And later he adds, "In the cases in which transitory spontaneous glucosuria occurs, the output of sugar tends to be small, under 1 per cent.; it may be present on a single day only or on several successive days, or it may recur at intervals." This is also in accord with H. Straus.[8]

The results of the present study lead to the same conclusion, and it is very probable that the failure to find glucosuria has been due to lack of care in searching for it, and also the failure to search daily over long intervals.

METHOD OF STUDYING CASES, AND TECHNIC

In all, twenty-seven cases of hyperthyroidism were studied. These varied from very severe to extremely mild ones, but all had sufficient symptoms or history or both to warrant the diagnosis.

To control these observations, twenty-five other individuals have been studied. These include healthy adults and patients convalescing from various diseases. Each case has had at least one blood-sugar determination and some have had many. Blood was always taken at a fixed time after breakfast, in most instances three hours and in some cases two and a half hours. In several cases the blood sugar was also estimated before breakfast when the stomach was empty.

3. Rosenberger, Franz: Die Ursachen der Glykurie, ihre Verhüntung und Behandlung, München. Müller, 1911.
4. Allen, F. M.: Studies Concerning Glucosuria and Diabetes, Boston, Leonard, 1913, p. 144.
5. Magnus-Levy in von Noorden: Metabolism and Practical Medicine, iii, 983.
6. Schulze, Fritz: Beitr. z. klin. Chir. (Bruns'), 1912, p. 207.
7. Garrod: Lancet, London, 1912, i, 629.
8. Straus, H.: Deutsch. med. Wchnschr., 1897, xxxiii, 309.

Jacobsen has shown that in normal individuals, after feeding 100 gm. of glucose or 100 gm. of starch in the form of bread, there is a rise in the blood sugar as compared with the preformed values. This rise occurs often in the first five minutes, reaches its height in half an hour, and then gradually returns to the level of the preformed value and often lower. On an average, this occurred in two hours, sometimes in three quarters of an hour, and in one case not until three and a half hours after.

Tachau[9] claims a return to fasting blood-sugar level as early as one hour after the administration of 100 gm. of glucose, but he contrasts fasting values with the values of other normal individuals observed one hour after 100 gm. of glucose.

The evidence so far certainly points to the fact that in normal individuals and in convalescents in whom there is no reason to suspect derangement in carbohydrate metabolism, the blood sugar, after an ordinary hospital breakfast averaging 75 gm. of carbohydrate with protein and fat, will return to the fasting level in less than three hours, and in most cases in less than two hours. The same holds true for the administration of 100 gm. of glucose when given fasting. There are exceptions to this, but they are few, as Table 1 will show.

All blood-sugar determinations in this table, as in the following table were made with from 10 to 20 c.c. of blood. In nearly all instances, duplicate samples of blood were employed as a control on the technic. The method of removing coagulable protein from the blood was that of Rona and Michaelis, while the sugar was estimated in the filtrate by the Bertrand method; this is probably the most accurate method known for the estimation of the reducing substances in the blood. Glucose was given, when not otherwise indicated, fasting, in lemon juice, 10 c.c., and water up to 150 c.c.

The patients' urine was examined for the appearance of spontaneous glucosuria in twenty-four hour specimens, and after administration of glucose, at two-hour intervals as indicated in the table.

Fehling's reaction and fermentation were used in the qualitative tests for sugar in the urine, but no tests are reported positive unless they also showed glucozazone crystals. A word with regard to the Fehling reaction: I have tried many of the qualitative tests for sugar, but have found none so satisfactory as the Fehling when done carefully and accurately with quantitative pipets and freshly prepared solutions.

In Table 1, the first ten subjects are all men leading a life of moderate physical activity. Cases 1, 2, 3 and 4 were studied from

9. Tachau: Deutsch. Arch. f. klin. Med., 1911, civ, 437.

TABLE 1.—Blood-Sugar Determinations in Twenty-Five Control Cases

Case	Name	Sex	Age	Date	Diagnosis	Blood-Sugar Percentage						Urine at 2-hr. Intervals Post 100 gm. Glucose, Three Specimens	Daily 24-Hr. Urine
						Fasting	1 Hr. p. c.*	2 Hrs. p. c.	2½ Hrs. p. c.	3 Hrs. p. c.	2 Hrs. Post 100 gm. Glucose		
1	M. S.	♂	27	7/29/14	Normal	....	....	....	....	.082	....		Sugar free (3 days)
				7/31/14		....	....	....	....	....	.089	10-12, 12-2 = no sugar	
2	H. A. B.	♂	28	7/29/14	Normal	....	....	.057	....	....	....		Sugar free (2 days)
				7/31/14		....	....	....	....	....	.092	8-10, 10-12, 12-2 = no sugar	
3	H. R. G.	♂	31	8/10/14	Normal	....	....	....	....	.087			
				8/12/14		....	....	....	....	....	.084	8-10, 10-12, 12-2 = no sugar	Sugar free (8 days)
				4/ 6/15		....	....	.075					
4	G. M.	♂	28	8/10/14	Normal	....	....	....	.084				
				8/11/14		....	....	....	.087	....	....		Sugar free (2 days)
				9/25/14		....	....	....	....	....	.088		
5	A. B. C.	♂	29	4/ 7/15	Normal	.095	....	....	....	....	....		Sugar free (2 days)
6	J. P.	♂	27	3/31/15	Normal	.086	....	....	....	....	....		Sugar free (4 days)
7	H.-V.	♂	27	3/31/15	Normal	.083							
8	H. L.	♂	27	4/ 7/15	Normal	.094							
9	H. S.	♂	27	4/ 9/15	Normal	.086							
10	W. T. L.	♂	37	4/23/15	Normal	.077							
11	E. M.	♀	29	4/18/15	Hyperchlorhydria	.088	.096	....	....	.081	....	9-11, 11-1, 1-3 = no sugar, post hospital breakfast	Sugar free (11 days)
12	A. F.	♀	53	4/28/15	Sciatica and constipation	.079	.118	....	....	.094	....	8-10, 10-12 = no sugar, post hospital breakfast	Sugar free (3 days)
13	L. B.	♀	18	4/30/15	Cardiac (conv.)	.086	....	....	....	.088	....	100 gm. glucose and breakfast: 8-10, 10-12, 12-2 = no sugar	Sugar free (3 days)

* Post cibum (after eating).

14	M. M.	♂	38	5/ 7/15	Pneumonia (conv.)	.072	.082	....	....	.07	....	9-11, 11-1, 1-3 = no sugar, post hospital breakfast	Sugar free (2 days)
15	R. W.	♂	28	12/11/13	Multiple neuritis	....	....	....	.080	....	....		Sugar free (3 days)
				12/13/13	.....	....	....	....	....	....	.071	7-9, 9-11, 11-1 = no sugar	
16	T. G.	♂	47	12/19/13	Chr. arthritis knee	....	....	....	....	.085	....		Sugar free (4 days)
				12/24/13	.....	....	....	....	....	....	.096	7-9, 9-11, 11-1 = no sugar	
17	S. E.	♀	26	3/ 5/13	Conv. rheumatism	....	....	....	....	.083			Sugar free (6 days)
				3/ 8/13	.....	....	....	....	....	....	.090	7-9, 9-11 = no sugar	
18	L. A. B.	♂	33	3/18/13	Cholelithiasis...	....	....	....	....	.087			
				3/20/13	Convalescent...	....	....	....	....	....	.077	7-9, 9-11, 11-1 = no sugar.....	Sugar free (3 days)
19	G. T.	♂	40	1/15/14	Bronchopneumonia (conv.)	....	....	....	.072				
				1/17/14	.....	....	....	....	....	....	.139	7-9, 9-11 = no sugar.....	Sugar free (4 days)
20	A. S.	♀	27	4/ 3/13	Conv. tonsillitis	....	....	....	....	.073	....		Sugar free (3 days)
				4/ 5/13	.....	....	....	....	....	....	.055	7-9, 9-11, 11-1 = no sugar	
21	B. M.	♂	25	2/26/14	Paroxysmal tachycardia	....	....	....	....	....	.091	8-10, 10-12, 12-2, 2-4 = no sugar.....	Nine exams.; no sug.
				3/ 5/14	Convalescent...	.004							
22	N. K.	♀	50	6/24/13	Retroversion uterus; neurasthenia	....	....	....	.097				
				6/27/13	.....	....	....	....	....	....	.094	7-9, 9-11, 11-1 = no sugar.....	Sugar free (4 days)
23	R. B.	♀	23	5/11/14	Nephroptosis; neurasthenia	....	....	....	.091				
				5/ 9/14	.....	....	....	....	....	....	.125†	8-10 = sug. ++; 10-12 = sug. ++; 12-2 = sug. ft. tr.	Twelve exams.; sugar 3 times
24	A. C.	♂	34	2/12/14	Paroxysmal tachycardia	....	....	....	.092				
				2/13/14	.....	....	....	....	....	....	.093	7-9 = sug. ft. tr.; 9-11 = no sugar; 11-1 = no sugar	Two exams.; sugar ft. tr. once
25	E. M.	♀	21	7/22/14	Gastroptosis....	....	....	....	....	.083			
				7/24/14	.....	....	....	....	....	....	.115	7-9 = sug. ft. tr.; 9-11, 11-1 = no sugar	Sugar free (4 days)

† 1 hr. p. 100 gm. glucose.

two to three hours after a meal (breakfast), and two hours after 100 gm. of glucose given fasting. In none of these cases was there a hyperglycemia or any sugar found in the urine. In one case (Case 2) there was a very low blood-sugar reading obtained two hours after breakfast, while that obtained two hours after 100 gm. of glucose was almost twice as high, and yet there was no sugar in the urine, at this time or at any other time.

In the next six cases (Cases 5, 6, 7, 8, 9 and 10), the determinations were made fasting only, and the average reading was 0.087 per cent., while the extremes were from 0.077 per cent. to 0.095 per cent. These cases were studied simply to confirm the observations of others, that the blood-sugar level of normal persons was approximately the same from two and a half to three hours after a meal as on a fasting stomach. The average of the first four cases taken after a meal was 0.079 per cent., and if Case 2 be excluded, 0.082 per cent. As will be seen, the average reading from two to three hours after a meal is lower than fasting.

The following four cases (Cases 11, 12, 13 and 14) were studied with a view to determining the blood-sugar curve, beginning before a meal (breakfast) and extending over a three hour period. One person (Case 13) was given 100 gm. of glucose with breakfast. All of these patients were ambulant convalescents and clinically cured. None of them had, even during the first part of their stay in the hospital, been very ill, and there was no reason to suspect any lowering or increase in their carbohydrate tolerance. The fasting blood sugar averages about the same, 0.082 per cent., as in the normal cases. An alimentary rise is seen in three cases one hour after breakfast, which returns to normal or below, three hours after the meal. Case 12, though showing a higher blood sugar than before breakfast, is still well within normal limits. None showed an alimentary or spontaneous glucosuria.

The next eight cases in this table are for the most part convalescent patients, in whom there was no reason to suspect a lowered carbohydrate tolerance. Cases 15, 16, 17, 18, 19, 20, 21 and 22 all showed from two and a half to three hours after breakfast and two hours after 100 gm. of glucose, blood-sugar readings which are approximately the same as in the strictly normal cases and well within normal limits. Case 19 is the only exception; here we have a very distinct hyperglycemia two hours after 100 gm. of glucose. There was no sugar in the urine collected over the test period, nor on four other examinations. The patient left the hospital the day following the last examination, and there was no opportunity for further study.

The last three cases given in this table are of separate and individual interest, as their study brought out some results, whch are analogous to those found in hyperthyroidism.

Case 23, particularly, showed a lowered tolerance to glucose, and brings up the question as to whether there was not some involvement of the suprarenals, the constant stimulation of which, owing perhaps to the nephroptosis, caused a lowered tolerance to carbohydrates. Certainly we cannot consider this a normal case, either clinically or from the standpoint of carbohydrate tolerance, and the well-known lowering of carbohydrate tolerance in pathologic conditions of certain of the endocrin glands is very suggestive.

In Case 24, although there was no actual hyperglycemia there was a definite lowering of carbohydrate tolerance as expressed by the glucosuria, and a possible hyperpermeability of the kidneys to sugar was suggested; but further study in this case was not possible.

In Case 25 the very slightly lowered tolerance to glucose is not explained. The patient was very nervous and poorly nourished.

A summary of Table 1 brings out the fact that in none of the cases, excluding, of course, the last three, was there any glucosuria, either spontaneous or alimentary. This is not in accord with Jacobsen's fifteen "normal cases," eight of whom showed an alimentary glucosuria after 100 gm. of glucose. The reason for this discrepancy is not entirely clear, unless it be the fact that in all his "normal cases," glucose was given, from two to four and a half hours after a meal and not fasting, and also that he includes cases among his "normals," whose blood-sugar readings vary from 0.083 per cent. to 0.128 per cent., as many as seven of the eight being 0.1 per cent. or over before 100 gm. of glucose were given. But as the Bang method, by which he estimates sugar, gives uniformly higher results than the Bertrand, comparison with my figures is not possible.

In Table 2 are given twenty-seven cases of hyperthyroidism. The first twenty range from cases of moderate severity to very severe ones, while the last seven in the table were very mild, and in one case, A. P. (Case 24), there was some doubt as to the diagnosis. A majority of the symptoms, however, pointed to hyperthyroidism. The remaining seven cases gave very definite histories of this disease, but most of the symptoms were much diminished or absent at the time of examination. They are given here to emphasize the point that lowered tolerance to carbohydrates may, with other symptoms of this disease, be considerably diminished or disappear entirely, over long periods of time.

From the results given in Table 1, it is clear that with the methods used, over 0.1 per cent. of blood sugar is to be regarded as hyperglycemia, provided, of course, that the blood is taken fasting or from two and a half to three hours after breakfast. The cases in which readings over this percentage are consistently seen have given either

TABLE 2.—Blood-Sugar Determinations in Twenty-Seven Cases of Hyperthyroidism

Case	Name	Sex	Age	Date	Blood-Sugar Percentage					Urine at 2-hr. Intervals Post 100 gm. Glucose, Three Specimens	Daily 24-Hr. Urine and Comments
					Fasting	1 Hr. p. c.	2½ Hrs. p. c.	3 Hrs. p. c.	2 Hr. Post 100 gm. Glucose		
1	D. M.	♀	32	1/27/13	....	....	.112	....	....		Sugar tr. to ft. tr. 4 times in 29 exams.
				2/ 7/13	....	....	....	....	....	7-9 = sugar 0.8%; 9-11 = sugar 0.3%; 11-1 = sugar 0.3%	
				2/10/13	....	....	....	....	.120	7-9 = sugar tr.; 9-11 = sugar tr.; 11-1 = sugar tr.	
2	H. R.	♀	34	2/28/13	....	....	....	.132	....		13 exams. sugar 3 times (ft. tr.)
				3/ 3/13	....	....	....	....	.160	7-9 = sugar 0.6%; 9-11 = sugar 0.3%; 11-1 = sugar 0	
			PO	3/24/13	....	....	....	.117			
				3/25/13	....	....	....	....	.128	7-9 = sugar ft. tr.; 9-11 = sugar ft. tr.; 11-1 = sug. 0; 1-3 = sug. 0	
3	R. R.	♀	40	4/ 7/13	....	....	....	....	.112	7-9 = sug. tr.; 9-11 = sug. 0	29 exams. sugar tr. 8 times
				4/16/13	....	....	....	.106			
				5/12/13	....	....	....	.126	....		Febrile (pulm. tbc.)
4	A. G.	♀	26	4/22/13	....	....	....	....	.125	7-9 = sug. +; 9-11 = sug. +; 11-1 = sug 0	23 exams. ft. tr. sugar 7 times
				5/ 1/13	....	....	....	.104			
				5/ 8/13	....	....	....	.120			
			PO	5/23/13	....	....	.097				
				5/27/13	....	....	....	....	.117	7-9 = sug 0; 9-11 = sug. 0	
5	A. M.	♀	22	5/22/13	....	....	....	.104			
				5/26/13	....	....	....	....	.140	7-9 = sug. ++; 9-11 = sug. +; 11-1 = sug. 0	18 exams. sugar once (ft. tr.)
				6/ 2/13	....	....	....	.091			
				6/ 5/13	....	....	....	....	.112	7-9 = sug. ++; 9-11 = sug. +; 11-1 = sug. +	
6	B. B.	♀	30	10/28/13	....	....	....	.086			
				10/29/13	....	....	....	....	.307	7-9 = sug. +++; 9-11 = sug. ++; 11-1 = sug +	15 exams. sugar + to ft. tr. 8 times
			PO	11/ 6/13	....	....	....	.112			
				12/ 5/13	....	....	.108				
7	A. S.	♀	21	11/20/13	....	.. .	.081	....	....		2 wks. after drop in temp. pulse remains up 2 exams. no sugar
				11/22/13	....	....	....	....	.071	7-9 = sug. 0; 9-11 = sug. 0; 11-1 = sug. 0	
				7/13/15	....	....	....	.100			
8	M. W.	♂	40	12/18/13	....	....	....	.109	....		45 exams. ft. tr. sugar 15 times
				12/22/13	....	....	....	....	.111	7-9 = sug. 0; 9-11 = sug. +; 11-1 = sug +	
				2/25/14	....	....	....	.106			
9	A. H.	♀	19	1/24/14	....	....	.083				
			PO								
				1/27/14	....	....	....	....	.088	7-9 = sug. 0; 9-11 = sug. 0; 11-1 = sug. 0	5 exams. no sugar
10	C. H.	♀	28	2/24/14	....	....	....	.133	....		49 exams. ft. tr. sugar 7 times
				3/12/14	....	....	....	....	.226	7-9 = sugar 1.8%; 9-11 = sugar 1.4%; 11-1 = sugar ft. tr.; 1-3 = sug. 0	
11	K. L.	♀	44	4/23/14	....	....	....	.115	....		26 exams. ft. tr. to quantitative amount 11 times
				5/26/14	....	....	....	....	.147	50 gm. glucose, 50 gm. bread, 50 gm. cereal: 8-10 = sug. +; 10-12 = sug. +; 12-2 = sug. +	
12	E. L.	♀	32	6/ 6/14	....	....	.107	....	....	Left hospital after four days' stay against advice	3 exams. no sugar
13	E. S.	♀	31	5/22/14	....	....	....	.108			
				5/24/14	....	....	.109	....	....		4 exams. ft. tr. sugar twice
14	M. S.	♀	23	9/19/14	....	....	.123				
				9/22/14	....	....	....	....	not obtained	7-9 = sug. +; 9-11 and 11-1 = sug. 0	8 exams. sugar 0

15	L. S.	♀	30	5/10/15	.106	....	....	....	....	138 gm. carbohydrate in diet	
				5/19/15	.107	.216	....	.168	....	100 gm. glucose + breakfast: 8-10 = sugar 1%; 10-4 = sug. tr.; 4 p. m. to 7 a. m. = sug. tr. 123 gm. carbohydrate in diet.	47 exams. sugar 5 times
				5/31/15	.117	....	....	.110	....	8-11 = sugar 1.3%; 11-1 = sug. tr.; 1-3 = sugar 0 (100 gm. glucose, fasting) 227 gm. carbohydrate in diet	
16	L. B.	♀	40	10/ 3/14	.113						
				10/ 8/14	....	....	....	....	.190	7-9 = sugar 0.5%; 9-11 = sug. ft. tr.; 11-3 = sug. ft. tr.	
				4/12/15	.104						
				4/14/15	....	....	....	....	.176	100 gm. glucose + breakfast: 8-10 = sug. ++; 10-1 = sug. 0	
			P O	4/21/15	.104	.106	....	.102	....	p. c. without glucose: 8-10 = sug. 0; 10-12 = sug. 0	
				4/30/15	....	....	....	....	.136	75 gm. glucose + breakfast: 8-12 = sug. +; 12-7 a. m. = sug. 0	60 exams. P. O. = sugar ft. tr. 3 times
				5/ 7/15	.082	....	....	....	....	200 gm. carbohydrate in diet past 4 days	
				6/ 7/15	.096	....	....	....	....	300 gm. carbohydrate in diet past 2 days	
17	D. W.	♀	31	3/ 5/15	.113	....	....	....	....	Further observation impossible, left hospital against advice	5 exams. sugar once
18	M. B.	♀	23	6/10/13	....	....	....	.117			
				6/19/13	....	....	....	.116	....		125 exams. sugar marked tr. to ft. tr. 41 times. This appeared more often before operation and after first operation than subsequently. Patient had 3 operations for thyroid condition
				6/25/13	....	....	.108	....	....	Had been on diet of 15 gm. carbohydrate for 5 days prev.	
				10/24/13	....	....	....	.114			
				10/28/	....	....	....	....	.115	7-9 = sug. ft. tr.; 9-11 and 11-1 = sug. 0	
				11/10/	....	....	....	....	.119	150 gm. glucose: 7-9 = sug. ++; 9-1 = sug. tr.; 1-3 = sug. 0	
			P O	11/15/14	....	....	....	.118			
				1/13/15	.107	....	....	....	....	150 gm. carbohydrate past 2 days	
				1/15/15	....	....	....	....	.144	8-10 = sugar 0.4%; 10-2 = no sugar	
				1/19/15	.073	....	....	....	....	After 3 days of 10 gm. carbohydrate in diet	
				1/29/15	.096	....	....	....	....	After 4 days of 102 gm. carbohydrate in diet	
19	E. M.	♀	43	5/19/15	.101	....	....	....	....		
				6/23/15	.125	....	....	....	....	9-11 = sugar 1.5%; 11-1 = sugar 1%; 1-3 = sugar 0.8%; 3-6, 6-8, 8-10 = sugar + 10 p. m. - 7 a. m. = sugar +; 7-12, 12-3, 3-6 = sugar + 6 p. m. - 7 a. m. = sugar tr.; 7-1 = sugar ft. tr.; 1-4 = no sugar	At end of 3 hrs. blood-sugar not obtainable. Left hospital. Showed sugar twice in 10 examinations
				7/17/15	.113	.224‡	....	....	....	8-10 = sugar 1.2%; 10-2 = sugar 0.5%	
20	M. C.	♀	43	2/16/14	....	....	.135	....	....		4 exams. ft. tr. sugar twice. Refused second phlebotomy
				2/ 7/						8-10 = sug. ++; 10-12 = sug. ++; 12-2 = sug. 0	
21	M. F.	♀	39	2/12/15	.095	....	....	....	....		8 exams. sugar 0. Thought to have beginning nephritis
				2/19/	....	....	....	....	.104	8-10, 10-12, 12-2 = sugar 0	
22	E. M.	♀	40	1/14/14	....	....	.097	....	....		12 exams. sugar 0.9% once
				1/20/	....	....	....	....	.113	7-9 = sug. ft. tr.; 9-11 = sug. ft. tr.; 11-1 = sug. 0	
23	S. S.	♀	55	1/23/15	.094	....	....	....	....		13 exams. no sugar. (urine always very scanty due to vomiting)
				2/ 6/	.115	....	....	....	....	Because of vomiting, glucose test could not be given	
24	A. P.	♀	58	9/30/14	....	....	....	.116	....		3 exams. no sugar. Discharge diagnosis = "dyscrasia of organs of internal secretion." Many of the symptoms pointed toward exoph. goiter; this seems the more probable diag.
				10/ 2/	....	....	....	....	.122	7-9 = sug. tr.; 9-11 = sug. marked tr.; 11-1 = sug. tr.	
25	G. N.	♀	25	2/11/15	.076	....	....	....	....		22 exams. no sugar
26	C. W.	♀	39	12/ 4/12	....	....	.097	....	....		11/13/12 to 12/21/12 sugar found every day from 0.4% to 0.7%. Carbohydrate intakes less than 60 gm.
				12/21/	....	....	.095				
27	L. R.	♀	22	4/21/13	....	....	....	.095	....		Very mild case. Operation showed colloid goiter
				4/24/13	....	....	....	....	.087	8-10, 10-12, 12-2 = no sugar	

* P. O. indicates postoperation.

spontaneous or alimentary glucosuria at some time during their stay in the hospital. This last statement does not apply to cases of diabetes, which, although they may be sugar-free in the urine, continue to show a hyperglycemia. Nor does it apply to certain cases of nephritis in which the hyperglycemia is probably due to an impermeability of the kidneys. Certain cases of myxedema studied in this connection also show quite marked hyperglycemia on thyroid treatment without the appearance of sugar in the urine. This last observation is one that is difficult to explain.

There are twenty of the severe or moderately severe cases. Eighteeen show a hyperglycemia, either fasting or from two and a half to three hours after breakfast. They all show either an alimentary or spontaneous glucosuria; in most of the cases both. And further, all those on whom the test was made show an increase above the pre-existing blood-sugar level two hours after 100 gm. of glucose, which was proportionally much greater than in any of the normal controls, most of whom showed a return to preformed values after this test. The alimentary glucosuria was usually quite marked, and in one patient persisted for three days.

In one case of the moderately severe type, Case 7, A. S., who did not show the foregoing changes, the patient was studied two or three weeks after the onset of symptoms and reacted precisely as did the normal controls. A year and a half later, although the symptoms were much milder, she showed 0.1 per cent. of blood sugar three hours after a very light breakfast. No opportunity has been offered to study the urine consecutively in this case. The other patient, A. H. (Case 9), had been operated on twice before she came under observation and, although improved as compared with her preoperative condition, still had active symptoms. She never showed any alteration in carbohydrate tolerance.

Of the mild cases, three show distinct lowering of the carbohydrate tolerance, as shown by alimentary and spontaneous glucosuria, and in two cases there was an alimentary hyperglycemia.

Case 26, C. W., showed a daily glucosuria for almost six weeks on a carbohydrate intake which never exceeded 60 gm. and very often was not more than 20 gm. This glucosuria was as high as 0.7 per cent. and yet the blood sugar never was above 0.097 per cent., two and a half hours after a light breakfast. It is unfortunate that this patient and A. C. (Case 24), in Table 1, who showed a faint trace of sugar, spontaneously and induced, were not studied at five or ten minute intervals after eating. It may be that their postprandial curves were very high and abrupt, as in some of Jacobsen's patients, and that during this time the kidney threshold for sugar was overstepped, or

that in certain individuals the kidney is permeable to sugar when the glycemia is within the limits of normal.

Cases 4, 5, 16 and 18 emphasize the point that, synchronous with decided clinical improvement, the tendency to hyperglycemia and glucosuria is reduced, lower blood-sugar values and a decreased tendency to glucosuria being noted in postoperative periods when temporarily, at least, the patient is much better.

The influence of diet, especially of carbohydrate food, is of some importance, as Jacobsen[10] and Strouse[11] have pointed out for both normal and pathologic cases. In the earlier cases it was not possible to control this accurately, but roughly the carbohydrate intake ranged from 100 to 300 gm., averaging 150 gm. daily. Lately accurate estimation of diets has been possible and in two cases, L. B. (Case 16) and M. B. (Case 18), their effect can be noted.

Patient 6, R. B., with very severe symptoms, who subsequently died after operation, shows a blood-sugar reading of 0.086 per cent. the day after admission to the hospital. She had been eating very little for some days, and this may explain the normal figures obtained. Always after this she showed marked intolerance to carbohydrates, and hyperglycemia.

The hyperglycemia and glucosuria produced by psychic stimuli, such as fear, emotion, etc., as shown in animals by Schaffer[12] and Cannon,[13] is to be considered in interpreting the foregoing results. That this factor would be more apt to influence cases of hyperthyroidism than normal individuals is self-evident. But even granting that venipuncture was responsible for the hyperglycemia found, it could hardly explain the alimentary or spontaneous glucosuria. Moreover, in all the cases studied, every precaution was taken to reassure patients, and evidences of undue excitement, such as increased pulse rate, nervousness, etc., were rarely seen. In one instance, R. B., Case 6, Table 2, noted above, whose intial blood-sugar reading was 0.086 per cent., showed as much apprehension if not more at this time than any of the other patients. And in this case the blood sugar was normal. M. B. (Case 18) and L. S. (Case 15) objected to venipuncture, but it never seemed to excite them.

There are various hypotheses which can be advanced to explain the production of hyperglycemia in hyperthyroidism: (1) the secretion of the thyroid acting on the suprarenals stimulating them to

10. Jacobsen, A. T. B.: Biochem. Ztschr., 1913, lvi, 471.
11. Strouse, Solomon: Bull. Johns Hopkins Hosp., 1915, xxvi, 211.
12. Schaffer, P. A.: Jour. Biol. Chem., 1914, xix, 296.
13. Cannon, W. B., Shohl, A. T., and Wright, W. S.: Am. Jour. Physiol., 1911, xxix, 280.

TABLE 3.—Blood-Sugar Determinations in Four Cases of Hypothyroidism

Case	Name	Sex	Age	Date	Diagnosis	Blood-Sugar Percentage						Urine at 2-hr. Intervals Post 100 gm. Glucose, Three Specimens	Daily 24-Hr. Urine
						Fasting	1 Hr. p. c.	2 Hrs. p. c.	2½ Hrs. p. c.	3 Hrs. p. c.	2 Hrs. Post 100 gm. Glucose		
1	M. K.	♀	..	6/23/14	Myxedema.....	....	....	....	.110				
				6/25/14	.....	....	....	....	....	....	.173	7-9 = sug. tr.; 9-11 = sug. v. ft. tr.; 11-1 = no sugar	Had been on thyroid ext. 6 wks. before observ. Symptoms of acute hyperthyroidism at time
2	A. F.	♀	..	1/26/15	Obesity.....	.053							
				1/28/15	Myxedema ?....	....	....	....	....	....	.111	150 gm. glucose: 7-9, 9-11, 11-1 = no sugar	No sugar (4 mos.)
				2/ 1/15	.....	....	....	....	....	....	.136	200 gm. glucose = no sugar; 8-10, 10-12, 12-2 = no sugar	Thyroid begun 2/4/15, stopped 4/9/15. Patient lost 21 lbs. Thyroid: started 5/5/15, stopped 5/24/15
				2/ 3/15	.....	....	....	....	....	....	.184	250 gm. glucose: 8-10 = sug. tr.; 10-12 = sug. ft. tr.; 12-2 = no sugar	
				2/14/15	.....	.112							
				2/19/15	.....	....	....	....	....	....	.170	8-10, 10-12, 12-2 = no sugar	
				3/13/15	.....	....	....	.159					
				3/15/15	.....	....	....	....	....	....	.129	8-10, 10-12, 12-2 = no sugar	
				3/19/15	.....	....	....	....	.117				
				3/27/15	.....	....	....	....	....	....	.138	7-9, 9-11, 11-1 = no sugar	
				4/ 2/15	.....	....	....	.116					
				4/14/15	.....	.106							
3	M. R.	♀	47	2/15/15	Myxedema.....	.080	....	....	....	....	....	Before thyroid treatment.....	No sugar (5 days)
				3/26/15	.....	.120	....	....	....	....	....	After thyroid treatment (8 days).....	No sugar (1 day)
4	J. H.	♂	38	10/ 3/14	Myxedema ?....	....	....	....	....	....	.068	8-10, 10-12, 12-2 = no sugar.....	No sugar, 2 exams.
				10/ 7/14	.....	....	....	....	....	....	.123†	8-10 = no sug.; 10-12 = marked tr. sug.; 12-2 = no sugar	

† After 200 gm. glucose.

increased activity; (2) an inhibitory action on the sugar-metabolizing powers of the pancreas; (3) it may produce its effect by action on some other of the endocrin glands concerned in sugar metabolism.

Allen[4] concludes that lowered tolerance to carbohydrates in exophthalmic goiter can be explained on a toxic or nervous basis, being more inclined to favor direct action of the thyroid secretion on the nervous system. Falta[14] favors the theory of direct action of the thyroid secretion on the pancreas.

It is not the purpose of the present article to discuss the various views pro and con on this subject, but whatever the mechanism of the production of hyperglycemia and general tendency to lowered tolerance for carbohydrates may be, there is one fact that stands out clearly from a study of Table 3, which is that thyroid extract produces in cases of hypothyroidism a very definite hyperglycemia, when, as shown in two cases, a low to normal blood sugar had previously existed (fasting). In Case 4, J. H., there was a low blood sugar two hours after 100 gm. of glucose, and a hyperglycemia two hours after 200 gm. of glucose. This patient did not receive thyroid extract. It is interesting to note that in the cases receiving thyroid extract the production of hyperglycemia was not accompanied by any toxic symptoms.

CONCLUSIONS

1. The normal blood-sugar values reported to date are as a rule much higher than those found in this paper. The extremes reported range from 0.04 per cent. to 0.13 per cent. Great diversity of methods and other factors mentioned above probably account for this. The general adoption of a uniform method for blood-sugar determinations is an urgent clinical need. A blood-sugar reading of 0.1 per cent. or over is to be considered a hyperglycemia.

2. Hyperglycemia is a very common accompaniment of hyperthyroidism. In the moderate and severe types of this disease, it occurs in 90 per cent. of the cases studied. In mild cases or during latent periods, normal blood-sugar values are commonly obtained.

3. Glucosuria, either spontaneous or alimentary (100 gm. of glucose), is an equally constant symptom, and encountered much more often than has been observed hitherto.

4. Alimentary hyperglycemia (two hours after 100 gm. of glucose) and alimentary glucosuria are found not uncommonly in the very mild cases, whereas hyperglycemia (fasting or postprandial) and spontaneous glucosuria are usually absent.

14. Falta: Quoted by Allen (Footnote 4).

5. As compared with normal individuals, there is a slower return to fasting blood-sugar values after doses of glucose have been given. This is more marked in proportion to the severity of the case.

6. Thyroid extract when fed to patients with myxedema, who previously showed normal blood-sugar values, produces hyperglycemia similar to that found in cases of hyperthyroidism.

7. The diagnostic significance of lowered tolerance to carbohydrates in hyperthyroidism is of great importance. The finding of glucosuria and hyperglycemia in other pathologic conditions, such as fever, alcoholism, asphyxia, neurasthenia and in the various endocrinopathies, somewhat nullifies its significance; but if these conditions can be excluded, its presence is highly suggestive.

THE PRODUCTION OF ATRIOVENTRICULAR RHYTHM IN MAN AFTER THE ADMINISTRATION OF ATROPIN *

FRANK N. WILSON. M.D.
ANN ARBOR, MICH.

INTRODUCTION

Atrioventricular rhythm has been investigated in the experimental animal by a large number of observers. Among these are Lewis,[1] Zahn,[2] Williams and James,[3] Ganter and Zahn,[4] Meakins,[5] Rothberger and Winterberg,[6] Eyster and Meek,[7] and others. It has usually been produced experimentally by slowing the rate at which the impulses are sent out from the sino-auricular node or by preventing the spread of such impulses to other parts of the heart. The following methods have been employed for this purpose: (1) cooling the sinus node with an ice pencil or by means of the ethyl chlorid spray, (2) crushing or excising the sinus node, or (3) isolating the sinus node by making cuts about it. Atrioventricular rhythm has also been produced by stimulation of the right vagus[1, 7] and by stimulation of the left accelerator.[6] We shall not discuss these observations in detail but wish to point out a few facts which they have established.

The reason why any of the above procedures may produce an A-V rhythm is plain when we understand that the A-V node, like the sinus node, has the property of elaborating impulses at regular intervals. Ordinarily this property of the A-V node is entirely latent because of the greater rhythmicity of the sinus node. The frequent stimuli which descend from the latter constantly destroy the stimulus material which accumulates at the A-V node before it has reached the level necessary

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* From the Department of Internal Medicine, University of Michigan.

1. Lewis, T.: The Effect of Vagal Stimulation upon Atrio-Ventricular Rhythm, Heart, 1914, v, 281.

2. Zahn: Experimentelle Untersuchungen am Saügetierherzen über Reizbildung und Reizleitung im Atrio-ventricularknoten, Arch. f. d. ges. Physiol., 1913, cli, 247.

3. Williams and James: Reversal of the Cardiac Mechanism, Heart, 1914, v, 109.

4. Ganter and Zahn: Experimentelle Untersuchungen am Saügetierherzen über Reizbildung und Reizleitung in ihrer Beziehung zum specifischen Muskelgewebe, Arch. f. d. ges. Physiol., 1912, cxlv, 335.

5. Meakins: Experimental Heart-Block with Atrioventricular Rhythm, Heart, 1914, v, 281.

6. Rothberger and Winterberg: Ueber die Beziehung der Herznerven zur Atrio-ventriculären Automatie, Arch. f. d. ges. Physiol., 1910, cxxxv, 559.

7. Eyster and Meek: Experiments on the Origin and Propagation of the Impulse in the Heart, Heart, 1914, v, 227.

for the formation of an impulse. The rate of the latent inherent rhythm of the A-V node has been called its "period" (Williams and James[3]). It may be very close to the rate of the sinus rhythm or it may be considerably below it. To produce A-V rhythm it is necessary either to reduce the rate of the sinus rhythm below the period of the A-V node or to increase the period of the A-V node above the rate of the sinus rhythm. The center which forms impulses most rapidly acts as pace-maker for the remainder of the heart. In most of the experimental studies previously referred to, A-V rhythm was produced by the first method: when A-V rhythm is produced by accelerator stimulation, however, the second method is the one employed.

Animal experimentation has also shown that most of the delay between auricular and ventricular systoles during the normal rhythm takes place within the A-V node (Hering[8]). Corresponding to these observations it has been found that in A-V rhythm the P-R interval of the electrocardiogram is reduced and the amount of reduction depends on the level in the node at which the abnormal rhythm originates. Depending on the site of origin, therefore, three types of A-V rhythm may be distinguished: in the first, which originates in the upper portion of the node, the P-R interval is present but reduced, in the second, which originates in a lower portion of the node, the P-R interval is zero, and in the third, which originates in the lowest portion of the node or in the main stem of the His bundle, the P-R interval is negative. It has also been shown by Meakins[5] that the auricular complex of the electrocardiogram in A-V rhythm is usually inverted. Two criteria, then, for the recognition of clinical A-V rhythm have been established experimentally: reduction or reverse of the P-R interval and inversion of P.

Clinically, atrioventricular rhythm is comparatively rare. There are two distinct varieties. The first of these is the heterogenetic type, or paroxysmal tachycardia of A-V origin, which is characterized by its rapid rate and the abrupt change in heart rate at the onset and end of an attack. During the abnormal rhythm the rate of the heart is not under the control of the extrinsic cardiac nerves. Paroxysmal tachycardia originating in the A-V node has been observed in man by Lewis,[9] by Cohn,[10] and by Rihl.[11]

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8. Hering: Nachweis dass die Vergögerung der Erregungsüberleitung zwischen Vorhof und Kammern des Saügetierherzens in Tawara'schen Knoten erfolgt, Arch. f. d. ges. Physiol., 1910, cxxxi, 572.

9. Lewis: Auricular Fibrillation and Its Relationship to Clinical Irregularity of the Heart, Heart, 1909-1910, i, 306; Paroxysmal Tachycardia, Accompanied by the Ventricular Form of Venous Pulse, Heart, 1910-1911, ii, 127.

10. Cohn: A Case of Paroxysmal Tachycardia, Heart, 1910-1911, ii, 170.

11. Rihl: Ueber atrioventriculäre Tachycardie beim Menschen, Deutsch. med. Wchnschr., 1907, xxxiv, 632.

The second variety of A-V rhythm is the homogenetic type which is characterized by its comparatively slow rate and by the very gradual change in heart rate at its onset and end. Moreover, the rate of the heart is under the control of the extrinsic cardiac nerves during the abnormal rhythm. A-V rhythm of this type has been observed in man by Lewis,[12] Belski,[13] Hume,[14] Williams and James,[3] Laslett,[15] Weil,[16] and others. It seems to be most common in acute infectious diseases, especially diphtheria. It has been produced in man by forced respiration[17] and by ocular pressure.[18] It has also been noted after the administration of atropin[18, 19] A-V rhythm of this type is comparable in every respect to that produced in animals by the methods previously mentioned.

In the present article we wish to describe a method by means of which A-V rhythm of the homogenetic type may be produced in a large proportion of young adults. In brief this method consists in stimulation of the vagus at a certain period of atropin action which begins about eight minutes after, and ends about twenty minutes after the hypodermic administration of 1 mg. of atropin sulphate. Our results indicate that at this period of atropin action the period of the A-V node closely approaches the rate of the sinus rhythm.

MATERIAL AND METHODS

The material for this report was obtained by the administration of atropin to eighteen men and two women between the ages of 20 and 28. Of these patients 1 to 13 inclusive were in good health and had no symptoms or signs referable to cardiac disease. Patients 14 to 17 inclusive complained of rapid heart action at times but had no other cardiac symptoms or signs. Patient 18 was under treatment for latent syphilis: there were no signs of heart involvement. Patients

12. Lewis: Clinical Electrocardiography, Londo , 1913, p. 73.
13. Belski: Beobachtungen über atrio-ventricu' Automatie im Verlauf der Infektionskrankheiten, Ztschr. f. klin. Med., 190 cvii, 515.
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19 and 20 had definite physical and electrocardiographical signs of heart disease and will be discussed separately.

Each patient, while under observation with the electrocardiograph, was given approximately 1 mg. of atropin sulphate by hypodermic injection and the movements of the galvanometer string were closely watched, and any change in heart mechanism observed was recorded photographically. If no change was noted records were taken at intervals of one or two minutes for from twenty to thirty minutes. At short intervals during the experiment the patient was asked to take a very deep breath and hold it, or pressure was made on the right eyeball. These procedures were carried out in an attempt to determine whether vagus stimulation during the early period of atropin action would produce in the normal heart an A-V rhythm, such as appeared spontaneously under this drug in two pathologic cases described later. The effect of vagus stimulation on the heart mechanism before the atropin was given was also determined.

PRODUCTION OF A-V RHYTHM IN YOUNG ADULTS WITH APPARENTLY NORMAL HEARTS

It was found that at a certain period of atropin action A-V rhythm could be produced in a large proportion of the cases investigated. In nine subjects it was produced by forced respiration, in two by right ocular pressure, and in one it appeared spontaneously. Ocular pressure, because of the discomfort that it produced, was employed in only a few cases. Five of our experiments were negative. In none of these cases could an A-V rhythm be produced by vagus stimulation before atropin had been given, although single idioventricular beats or considerable flattening out of the P wave sometimes occurred. The period of atropin action during which an A-V rhythm could be produced varied greatly, but usually the abnormal rhythm was most easily obtained between eight and fifteen minutes after the drug had been given. The exact period over which it could be produced was not determined because it was often impossible to recognize the abnormal rhythm by observing the movements of the galvanometer string, and continuous records were not taken. In a large proportion of the subjects forced respiration was repeated at intervals during the experiment until the abnormal rhythm could no longer be produced, which was usually about twenty minutes after the drug had been given. A-V rhythm could not be produced beyond this point and during the maximum effect of the atropin. The subjects were not selected except that young people were chosen.

TYPES OF A-V RHYTHM

The A-V rhythms obtained by this method may be divided into three classes: (a) A-V rhythm in which the P-R interval was present but reduced, (b) A-V rhythm in which the P-R interval was zero, and (c) A-V rhythm in which there was an R-P interval.

The first type of A-V rhythm was observed in nine subjects. It is illustrated in Figure 1. Figure 2 illustrates the normal mechanism before atropin and Figure 3 the normal mechanism after the atropin

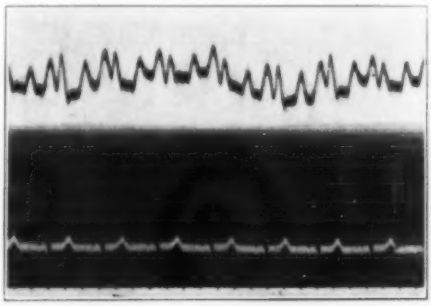

Fig. 1.—Subject 14, Lead 3. A-V rhythm of Type 1 which occurred spontaneously after atropin. P-R equals 0.13 second; a-c equals 0.15 second. Heart rate 94.

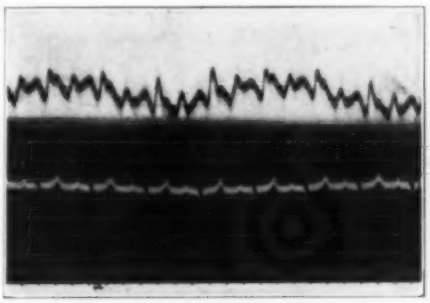

Fig. 2.—Subject 14, Lead 3. Taken before atropin was given. The P-R interval is 0.19 second. The a-c interval is 0.20 second. The heart rate is 94.

effect had reached its maximum. This A-V rhythm appeared spontaneously after atropin (Patient 14). The P-R and a-c intervals are reduced and P is inverted.

A-V rhythm of the second type is illustrated by Figure 4 from Patient 8. In this figure P is not seen during the abnormal mechanism because it occurs simultaneously with R as is shown by the tall composite *a* wave in the jugular pulse. The abnormal rhythm in this case

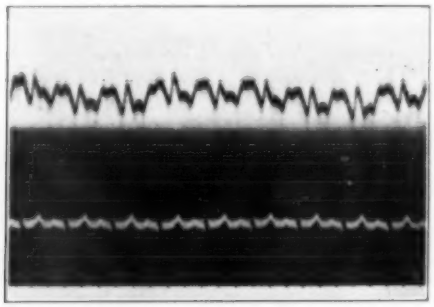

Fig. 3.—Subject 14, Lead 3. Normal rhythm at the time of the maximum atropin effect. Heart rate 112.

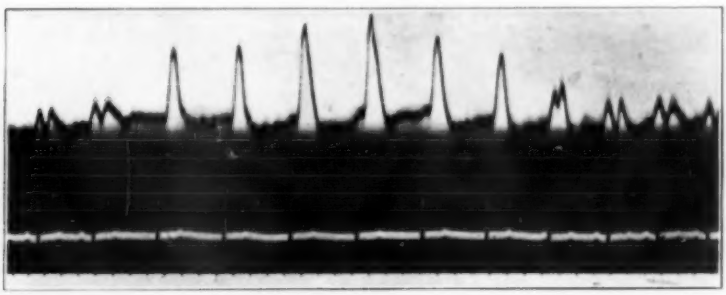

Fig. 4.—Subject 8, A-V rhythm of Type 2 produced after atropin by right ocular pressure. During the abnormal rhythm P is not seen but a large wave in the venous pulse shows that auricles and ventricles contracted simultaneously. Heart rate during the abnormal rhythm 78.

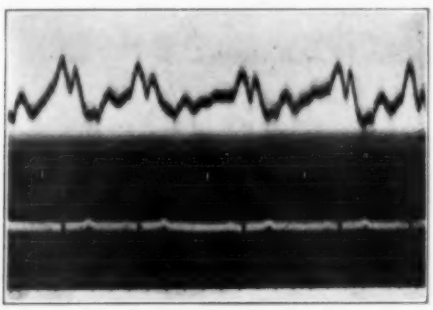

Fig. 5.—Subject 8, Lead 3. Taken before atropin was given. P-R equals 0.15 second; a-c equals 0.15 second. Heart rate 58.

was produced by right ocular pressure. Short periods of A-V rhythm alternated with short periods of normal rhythm for several minutes after the ocular pressure was made. In Figure 5 the normal rhythm before atropin is shown and in Figure 6 the heart mechanism at the time of the full atropin effect is seen. Figure 7 shows the effect of right ocular pressure before atropin. The third cycle is an idioventricular beat as there are no P nor *a* waves accompanying it. The a-c intervals of the sixth and eighth cycles are reduced showing that the ventricle escaped in each instance. It will be noted that there may be

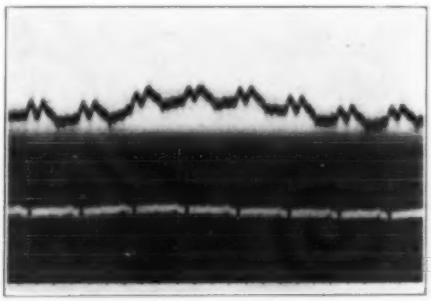

Fig. 6.—Subject 8, Lead 3. The normal rhythm at the time of the maximum atropin effect. Heart rate 100.

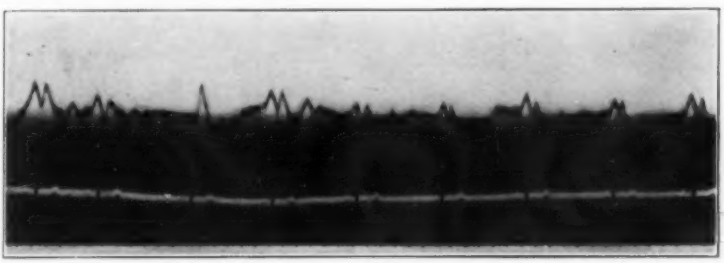

Fig. 7.—Subject 8, Lead 3. The effect of right ocular pressure before atropin. No A-V rhythm was produced but single idioventricular beats occurred (Cycles 3, 6 and 8). In Cycle 7 there is a marked flattening out of P without any corresponding change in the *a* wave.

very marked flattening out of the P wave of the electrocardiogram without any corresponding change in the venous pulse during vagal stimulation (Cycle 7), which confirms a view expressed by me in a previous article that this change in the shape and size of the P summit during vagal stimulation was not due to a diminution of the contractility of the auricles but to a change in the location of the pacemaker or an abnormal spread of the contraction wave over these chambers. An A-V rhythm of Type 2 was observed in five subjects.

The third type of A-V rhythm was observed in two subjects. It is illustrated by Figures 8, 9 and 10, all from Patient 7. P is inverted and follows R during the abnormal mechanism in Leads 2 (Fig. 9) and 3 (Fig. 10), and is invisible in Lead 1 (Fig. 8). In the venous pulse there is a tall wave which has a broader summit than those seen in Figure 4. In Figures 8 and 9 transitions from the abnormal to the normal mechanism are seen and the end of a transition from the normal to the abnormal mechanism is seen in Figure 9. It will be

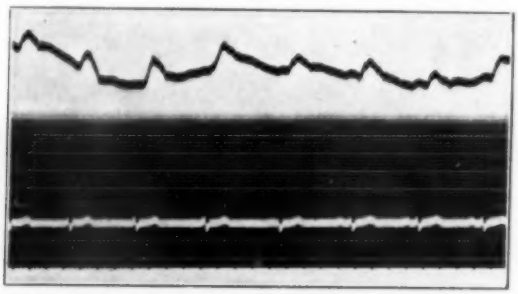

Fig. 8.—Subject 7, Lead 1. A-V rhythm produced by deep respiration during an atropin experiment. P is invisible during the abnormal rhythm.

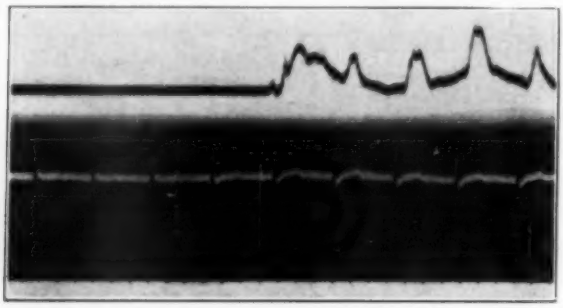

Fig. 9.—Subject 7, Lead 2. A-V rhythm of Type 3 produced after atropin by deep respiration. During the abnormal rhythm P is inverted and appears after R. The R-P interval is 0.05 second. The heart rate during the abnormal rhythm is 75. At the beginning of the figure the end of a transition from the normal to the abnormal rhythm is seen. P appears after R as a summit in the first two cycles.

noted that in the first two cycles of this figure P appears after R as a summit. This indicates that the auricular contractions which produced these Ps were responses to the sinus node rather than to the A-V node, as were those which followed, which are represented by inverted Ps. The normal mechanism in this case is shown in Figure 11, which was

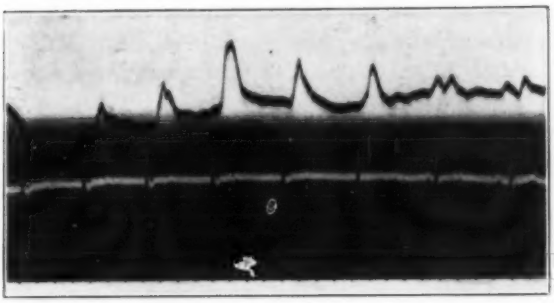

Fig. 10.—Subject 7, Lead 3. A-V rhythm of Type 3 produced by forced respiration after atropin. P appears after R and is inverted during the abnormal rhythm. In the venous pulse there is a single tall wave with a broad summit. A transition from the abnormal to the normal rhythm occurs.

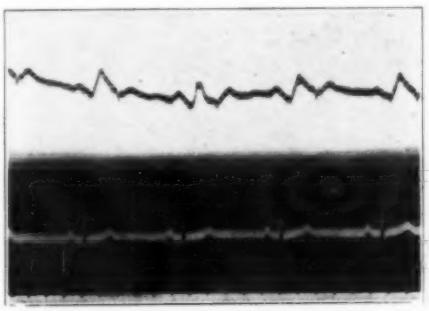

Fig. 11.—Subject 7, Lead 3. The normal rhythm before atropin. The P-R interval is 0.17 second. Heart rate 54.

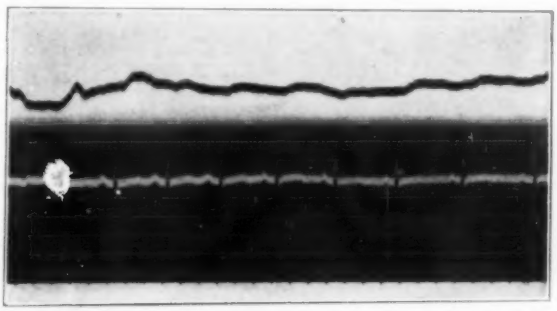

Fig. 12.—Subject 7, Lead 3. The effect of a deep breath 18 minutes after atropin. A-V rhythm is no longer produced by this procedure. There is still some vagus arrhythmia showing that the vagi are not completely paralyzed.

taken before atropin was given and in Figure 12 the effect of a deep breath eighteen minutes after atropin is shown. At this time the A-V rhythm could no longer be produced although the vagi were not completely paralyzed as is shown by the presence of some respiratory arrhythmia.

The accompanying table contains a summary of the experiments on persons with apparently normal hearts. In some subjects more than one type of A-V rhythm was observed; in Subject 9 Types 1 and 2 both occurred and in Subject 13 all three types were recorded.

Summary of Experiments on Persons with Apparently Normal Hearts

Subject	A-V Type	A-V Rhythm P-R sec.	A-V Rhythm a-c sec.	S-A Rhythm P-R sec.	S-A Rhythm a-c sec.	A-V Rhythm Rate	S-A Rhythm Rate Before Atropin	S-A Rhythm Rate at End of Exper.
1	1	0.13	0.15	0.15	....	54	85	92†
2	1	0.13	....	0.16	....	66	63	70
3	1	0.16	0.19	0.19	0.21	60	52	60†
4	1	0.12	....	0.14	....	80	75	†
5	0*	....	....	....	....	..	..	..
6	2	0.00	....	0.17	....	66	75	109
7	3	0.05	....	0.17	....	75	54	100
8	2	0.00	0.00	0.15	0.15	78	58	100
9	1	0.11	0.13	0.15	0.17	63	60	73
..	2	0.00	0.00	0.05	0.17	66	..	..
10	2	0.00	0.00	0.16	0.19	92	75	92
11	1	0.15	....	0.17	....	80	85	100
12	0*	....	....	....	....	..	..	...
13	1	0.10	....	013	....	75	75	85†
..	2	0.00	....	0.13	....	100	..	...
..	3	0.05	....	0.13	....	109	..	...
14	1	0.13	0.15	0.19	0.20	94	94	112
15	1	0.13	0.13	0.15	0.15	100	100	109
16	0*	....	....	....	....	...	...	...
17	0*	....	....	....	....	...	...	...
18	0*	....	....	....	....	...	...	...

* No A-V rhythm was produced.

† A-V rhythm could still be produced when the experiment was terminated.

The rate of the abnormal rhythm was usually intermediate between the normal rate before atropin and the sinus rate after the atropin effect had reached its maximum. The rates given in the table are only approximate, as the constant forced respiration during most of the experiments caused very marked fluctuations in heart rate even when the abnormal rhythm was present. These fluctuations made it impossible to compare the rate of the sinus rhythm and the rate of the A-V rhythm during the period when the latter could be produced. The A-V rhythm sometimes persisted for a very short period and was quickly replaced by the normal rhythm at a more rapid rate. Even when the abnormal rhythm appeared spontaneously it usually alternated with periods of normal rhythm and the heart rate varied constantly.

THE SPONTANEOUS APPEARANCE OF A-V RHYTHM AFTER ATROPIN IN TWO PATHOLOGIC CASES

In Patients 19 and 20 an A-V rhythm developed spontaneously after the administration of atropin. The complete histories and examinations of these patients have been given elsewhere[17] and need not be repeated here. Patient 19 was a young man aged 22 who complained of occasional periods of rapid heart action. The examination of the

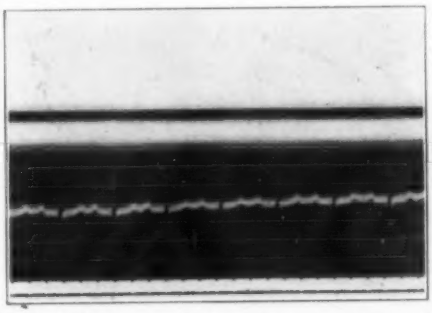

Fig. 13.—Subject 19, May 15, 1915; Lead 3. The normal rhythm before atropin. P-R equals 0.26 second.

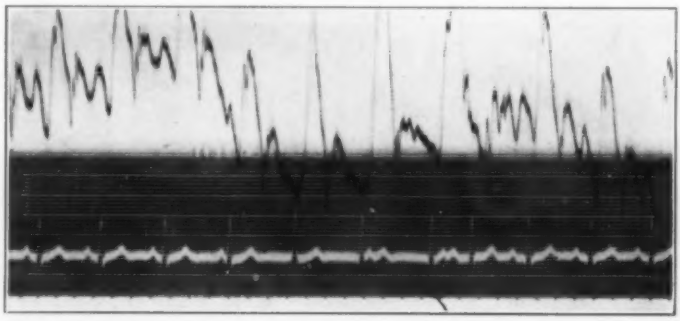

Fig. 14.—Subject 19, May 15, 1915; Lead 2. A period of auriculoventricular dissociation which occurred spontaneously after atropin. This dissociation begins with the fourth cycle and continues until P falls between R and T (Cycle 7). The eighth ventricular complex occurs as a response to the P which falls between R and T of the seventh cycle. During the period of dissociation the ventricles contract more rapidly than the auricles.

heart was negative except for the electrocardiographic tracings which showed a marked prolongation of the P-R interval when the patient first came under observation. At this time deep respiration produced on some occasions auriculoventricular dissociation which was not entirely due to the heart-block present but to an increase in the rate of

the idioventricular rhythm. During these periods of dissociation the ventricles beat more rapidly than the auricles. The P-R interval at the time of the first examination (Fig. 13) was 0.33 second.

One month after this observation was made the patient was again examined and the P-R interval was found to be only 0.26 second in duration. At this time no auriculoventricular dissociation could be

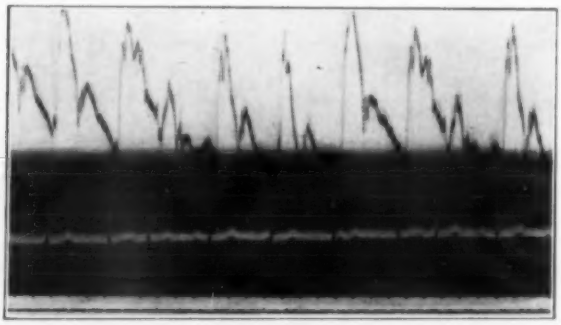

Fig. 15.—Subject 19, May 15, 1915; Lead 3. A period of auriculoventricular dissociation like that in Figure 14. The first ventricular complex which follows a period of dissociation is aberrant (ventricular complexes 3 and 8) and the P-R interval of these cycles is increased.

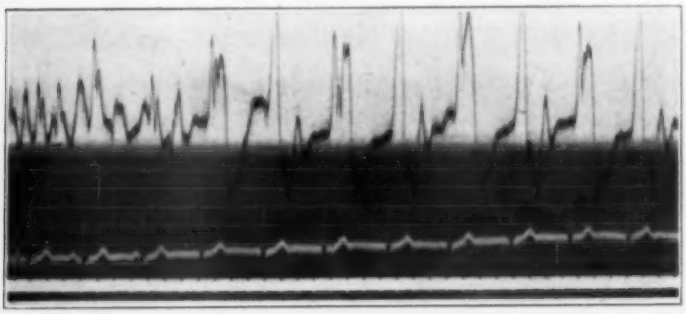

Fig. 16.—Subject 19, May 8, 1915; Lead 2. A period of auriculoventricular dissociation similar to those seen in Figures 14 and 15, except that the heart mechanism is complicated here by interference between the stimuli arising in the sinus node and those arising in the junctional tissues. The P waves which fall between R and T are deformed and sometimes diphasic (Cycle 6).

produced by deep respiration. The patient was given atropin (1 mg.) hypodermically and periods of dissociation similar to those previously described appeared spontaneously about eight or nine minutes after the drug was given. This mechanism is illustrated in Figure 14. It will be seen in this figure that, because of escape of the idioventricular

rhythm, P gradually approaches R and finally falls between R and T (Cycles 6 and 7). When P has reached this position the ventricles respond to the auricles (Cycle 8) and both chambers beat in unison for several beats after which the same process is repeated.

The first ventricular contraction which followed such a period of dissociation (Cycle 8, Figure 14) was often characterized by an aberrant ventricular electric complex (Cycles 3 and 8 of Fig. 15) and

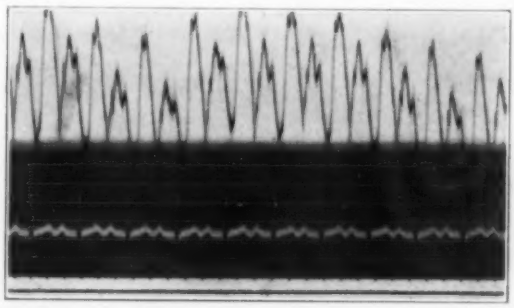

Fig. 17.—Subject 19, May 15, 1915; Lead 2. The heart mechanism at the time of the maximum atropin effect. The P-R interval is still 0.25 second, showing that the block present in this case is organic.

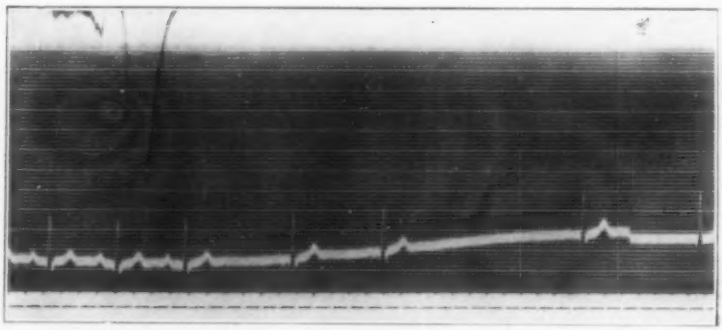

Fig. 18.—Subject 19, May 29, 1915; Lead 2. The effect of right ocular pressure. The duration of the pressure is indicated at the top of the curve. There is marked flattening out of the P waves during vagus inhibition. The P-R interval of the normal rhythm (first two cycles) is now 0.21 second. No A-V rhythm was produced by ocular pressure.

the As-Vs time of these cycles was always increased (Figs. 14 and 15). The failure of the stimuli arising at the sinus node and those arising in the junctional tissues to produce interference phenomena, which is the cause of this peculiar heart mechanism, may be explained by assuming that it was more difficult for stimuli to pass from the ven-

tricular side of the junctional tissues to the auricles than in the opposite direction. On some occasions such interference did occur, probably as a result of some change in the degree of block. When this happened the Ps which fell between R and T were deformed and sometimes diphasic (Fig. 16). The maximum atropin effect at the time of the second examination is shown in Figure 17. The P-R

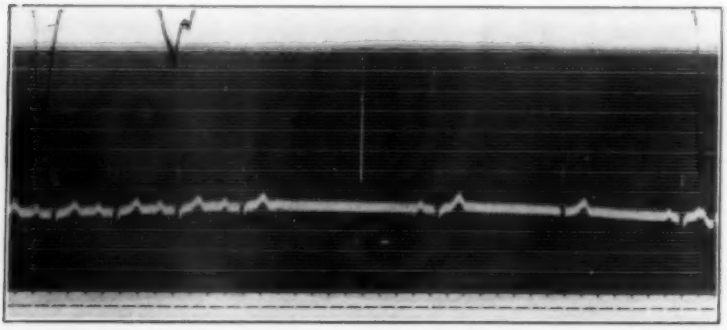

Fig. 19.—Subject 19, May 29, 1915; Lead 2. The effect of left ocular pressure. No A-V rhythm is produced. A single idioventricular beat is seen (Cycle 6).

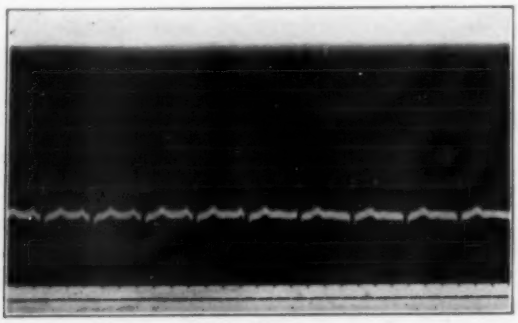

Fig. 20.—Subject 19, May 29, 1915; Lead 2. A-V rhythm of Type 2 which appeared spontaneously after atropin.

intervals in this figure are still 0.25 second indicating that the block present in this case was organic.

The patient was examined a third time one week after the second examination. The P-R interval at this time was 0.21 second. On this occasion an attempt was made to produce the abnormal mechanism by ocular pressure. The results of these experiments are shown in Figures 18 and 19. Single idioventricular beats are seen but no

definite A-V rhythm was produced. There was a marked flattening out of the P summits as a result of right vagus pressure (Fig. 18) due either to dislocation of the pace-maker or to interference phenomena. Atropin (1 mg.) was given hypodermically and about eight or nine minutes later an A-V rhythm of the type described as Type 2 appeared spontaneously (Fig. 20). This rhythm could be slowed slightly by ocular pressure (Fig. 21) showing that the A-V node was

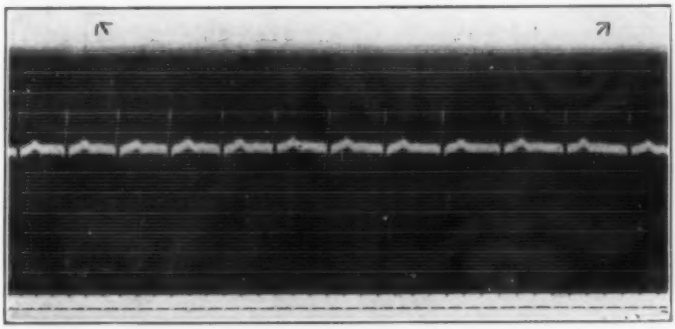

Fig. 21.—Subject 19, May 29, 1915; Lead 2. A-V rhythm of Type 2 which appeared spontaneously after atropin is slowed by left ocular pressure showing that the A-V node is still partially under vagus control.

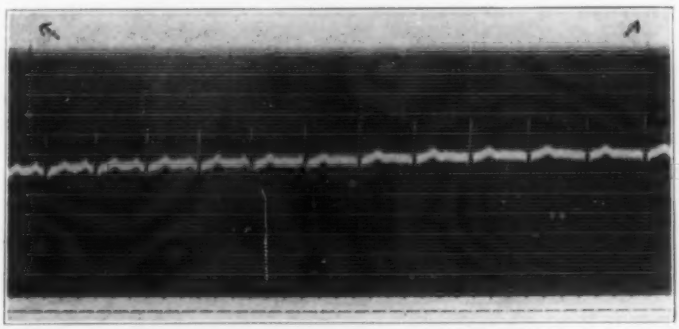

Fig. 22.—Subject 19, May 29, 1915; Lead 2. After the A-V rhythm had given place to the normal rhythm it could still be produced by right ocular pressure. The duration of the pressure is indicated by arrows.

still partially under vagus control. When the A-V rhythm gave place to the normal rhythm it could again be produced by ocular pressure either upon the right or left eye (Figs. 22 and 23). The complete atropin effect was not obtained at the time of the third examination but although the abnormal rhythm appeared spontaneously at first it

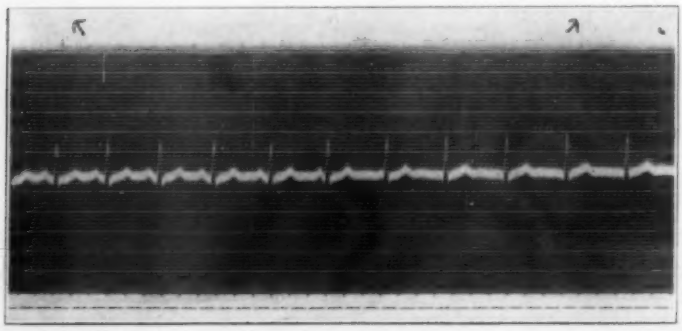

Fig. 23.—Subject 19, May 29, 1915; Lead 2. Same as previous figure except that the left ocular pressure was used instead of right ocular pressure.

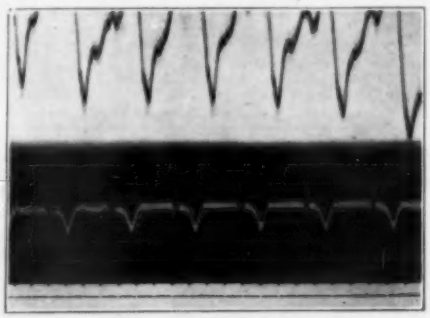

Fig. 24.—Subject 20, Lead 3. A-V rhythm of Type 2 which appeared spontaneously about eight minutes after atropin. The ventricular complexes are abnormal, but different from those of the following figure. P is not seen because it is buried in R.

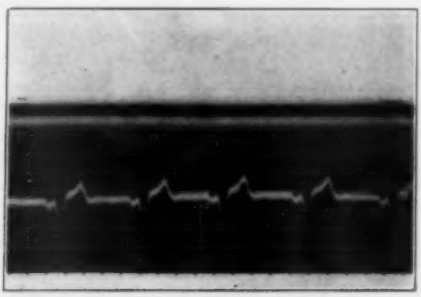

Fig. 25.—Subject 20, Lead 3. The rhythm before atropin. P is inverted and the P-R interval is 0.10 second indicating that an A-V rhythm of Type 1 is present. The ventricular complexes are abnormal because of right branch bundle block.

was afterward only present after ocular pressure. The comparatively slight block which was present at the time of the last examination was probably responsible for the appearance of a typical A-V rhythm in place of the peculiar periods of auriculoventricular dissociation which were observed under atropin when the block was more marked.

Case 20 was a very complex one and will be discussed fully in another place. The patient was a young man aged 23, who suffered from attacks of paroxysmal tachycardia and who had the physical signs of mitral stenosis. The electrocardiograms showed at times the presence of an A-V rhythm of Type 1 which was complicated by a right branch bundle block. During atropin experiments an A-V rhythm of Type 2 appeared spontaneously about eight minutes after the drug was given and alternated with the normal rhythm and the A-V rhythm of Type 1 for several minutes, after which it gave place to the normal

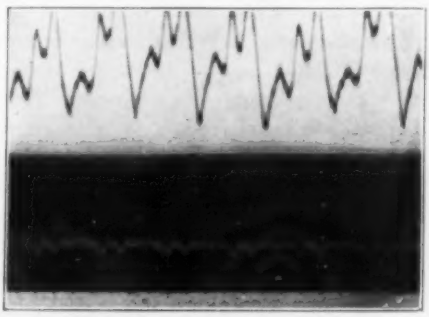

Fig. 26.—Subject 20, Lead 3. The normal rhythm at the height of the atropin effect. P is upright, the P-R interval is 0.17 second and the ventricular complexes are normal.

rhythm and appeared no more until the next atropin experiment was made. This rhythm is illustrated in Figure 24. It differs from the other rhythms of Type 2 described in this article in that the ventricular complexes are abnormal. The significance of these abnormal complexes will be discussed elsewhere. The heart mechanism in this case before atropin is shown in Figure 25 and the normal rhythm which appeared at the height of the atropin action is seen in Figure 26

DISCUSSION

The special susceptibility of the heart toward A-V rhythm during the intermediate period between the hypodermic administration of atropin and the appearance of its maximum effect may be explained in the following way: Atropin increases the heart rate by paralyzing the vagus endings in the heart and thus liberating the sinus node from

the inhibitory effect ordinarily exercised by this nerve. The vagus, however, is not distributed to the sinus node alone but also to other portions of the heart and especially to the special structures at the auriculoventricular junction. Atropin paralyses these endings also, as is shown by its effect on functional heart-block, and there is every reason to suppose that this drug increases the period of the A-V node in the same way in which it increases the rate of the sinus rhythm. Because of some selective action exercised by atropin on the vagus terminations in the A-V node, however, this node is released from vagus inhibition before the sinus node. It thus happens that at a certain period of atropin action the A-V node is partially released from vagus inhibition, while the sinus node is still relatively under vagus control. At this time the period of the lower node is increased so that it approaches or exceeds the rate of the sinus rhythm. When it exceeds it, A-V rhythm appears spontaneously. When it approaches without reaching the sinus rate A-V rhythm may be produced by some method of vagus stimulation. This slows the sinus rate markedly without exerting a corresponding effect upon the A-V node.

When the atropin effect has reached its maximum, however, the sinus node is also released from vagus control and at this time its inherent rhythm is much more rapid in rate than that of the A-V node and it can not be slowed by vagus stimulation, so that A-V rhythm can no longer be produced. Vagus stimulation does not produce A-V rhythm when atropin has not been given, because, although it slows the sinus rate, it also slows the period of the A-V node sufficiently to keep it below the rate of the sinus node and hence prevents the appearance of A-V rhythm. In exceptional cases in which the period of the A-V node is pathologically rapid or less sensitive than normal to vagus stimulation, ocular pressure or forced respiration does produce A-V rhythm[17] and it is not infrequent that single idioventricular beats occur in normal people as a result of the first of these procedures.

Other explanations might be offered for the production of A-V rhythm by the method described in this article. It is possible, for instance, that atropin may have some action upon the heart other than the well known paralysis of the vagi which it produces. It is also possible that ocular pressure and continued forced respiration, which were used in many of our experiments to produce A-V rhythm, may stimulate the accelerator nerves and thus tend to increase the period of the A-V node. The latter explanation would not account for the spontaneous appearance of A-V rhythm in some of the patients reported nor would it account for the fact that A-V rhythm cannot

be produced by these methods after the atropin effect has reached its maximum.

THE RELATION OF A-V RHYTHM TO PALPITATION

It remains to be mentioned that three patients (Nos. 8, 19 and 20) who developed A-V rhythms of Type 2 complained of marked palpitation during the abnormal rhythm. This palpitation was associated not with arterial throbbing but consisted in throbbing of the heart and a feeling of tension in the throat. It was probably due to the fact that the auricles and ventricles contracted simultaneously so that the auricles could not discharge their blood into the ventricles. but forced it back into the great veins. This palpitation is entirely comparable to that felt during attacks of paroxysmal tachycardia with a positive venous pulse and the cause is the same in both instances. It seems unlikely, however, that A-V rhythm of the type here described is a frequent cause of clinical palpitation.

SUMMARY

It was found possible to produce A-V rhythm in a large proportion of young persons by vagus stimulation during the intermediate period between the hypodermic injection of atropin and the appearance of its maximum effect. In three cases, one normal and two cardiac cases, A-V rhythm appeared spontaneously under this drug. In none of the individuals of the present series who had apparently normal hearts was it possible to produce A-V rhythm before the drug had been given. This was possible, however, in two patients with cardiac disease. It was not possible to produce A-V rhythm after the atropin effect had reached its maximum in any of the subjects investigated.

We believe that the special susceptibility of the heart toward A-V rhythm during the early action of atropin is due to a selective action of this drug on the vagus terminations in the A-V node, in that it paralyses these before it paralyses those in the sinus node.

In two pathologic cases the A-V rhythm which appeared after atropin exhibited unusual features.

Three patients complained of marked palpitation as a result of simultaneous contraction of auricles and ventricles during A-V rhythm.

A CASE IN WHICH THE VAGUS INFLUENCED THE FORM OF THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM *

FRANK N. WILSON, M.D.
ANN ARBOR, MICH.

BUNDLE-BRANCH BLOCK

In 1910, Eppinger and Rothberger[1] published electrocardiographic tracings illustrating the effects of dividing the right and left branches of the His bundle on the ventricular complex. Eppinger and Stoerk,[2] later in the same year, were able to report two clinical cases of bundle-branch block in which the diagnoses, made with the aid of electrocardiograms, were confirmed at section. Since that time similar cases have been reported by a large number of authors. Carter,[3] in his report of twenty-two cases, concludes that the ventricular complexes seen in cases of bundle-branch block exhibit, in contrast to normal ventricular complexes, the following characteristics. They are diphasic rather than polyphasic and are composed of (1) a primary deflection or QRS group, whose amplitude is greater than that of the normal ventricular complex and whose duration is longer, being one-tenth second or more; and (2) of a secondary deflection in the opposite direction from the first, an exaggerated T. The primary deflection usually comprises at least one-third of the entire ventricular complex and is often notched. These abnormal complexes, although produced by supraventricular stimuli, resemble very closely the electrical complexes produced by ventricular extrasystoles. When the block is in the right branch of the His bundle, as happens most often (twenty-one of Carter's twenty-two cases were of this type), the initial deflection is upward in Lead 1 and downward in Lead 3; and when the block is in the left branch the direction of the initial deflection in these leads is reversed. The fact that the right branch is so much more frequently affected than the left is probably due to its greater length

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* From the Department of Internal Medicine, University of Michigan.

1. Eppinger, H., and Rothberger, J.: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel der Reizleitungssystem, Ztsch. f. klin. Med., 1910, lxx, 1.

2. Eppinger, H., and Stoerk, O.: Zur Klinik des Elektrokardiogramms, Ztschr. f. klin. Med., 1910, lxxi, 157.

3. Carter, E. D.: Clinical Observations on Defective Conduction in the Branches of the Auriculo-ventricular Bundle, THE ARCHIVES INT. MED., 1914 xiii, 803.

before division. In most of the cases reported the bundle-branch block has been permanent, so that it has been impossible to compare the abnormal complexes with the normal complexes of the same case. In one of Carter's patients, however, the block was transient and such a comparison could be made, and in two of Mathewson's[4] patients transitions from the normal to the abnormal complexes were recorded electrocardiographically. In one of the patients reported by the latter, right and left bundle-branch block alternated irregularly with the normal mechanism.

EFFECT OF VAGI ON THE VENTRICULAR ELECTROCARDIOGRAM IN ANIMALS

Since the original experiments of Eppinger and Rothberger, abnormal ventricular complexes similar in form to those obtained by cutting one branch of the A-V bundle have been observed under a variety of experimental conditions. They may arise in at least three ways. First, they occur when there is a block in one of the branches of the His bundle even when the ventricles are responding to supraventricular stimuli. Second, they are found when heterogenetic beats or extrasystoles arise within the ventricles below the bifurcation of the A-V bundle. Third, they may occur when homogenetic beats arise in the branches of the His bundle. There is a possibility, of course, that the latter may originate within the walls of the ventricles outside the specialized tissues, but since it seems likely that homogenetic beats rarely if ever arise outside of the specialized tissues in the auricles, it is reasonable to suppose that the same is true of the ventricles.

Abnormal ventricular complexes of this type have occasionally been associated with stimulation of the vagi in animals. If heart block be produced experimentally by mechanical destruction of the A-V bundle, the ventricular complexes of the resulting idioventricular rhythm are always of the normal form. When, however, A-V dissociation is produced in animals by strong stimulation of the vagi, the ventricular complexes are often abnormal and typically diphasic. This was pointed out by Einthoven[5] as early as 1906 and similar observations have been made by Kahn[6] and by Kraus and Nicolai.[7] In such cases the ventricular contractions are of the homogenetic type since they always occur rhythmically and at a slow rate. We must assume,

4. Mathewson, G. D.: Lesions of the Branches of the A-V Bundle, Heart, 1912-1913, iv, 385.

5. Einthoven, W.: Le Telecardiogramme, Arch. internat. de physiol., 1906, iv, 132.

6. Kahn, R. H.: Beiträge zur Kenntnis des Elektrokardiogramms, Arch. f. d. ges. Physiol., 1909, cxxvi, 197.

7. Kraus, F., and Nicolai, G. F.: Das Elektrokardiogramm des gesunden und kranken Menschen, Leipzig, 1910.

therefore, that the vagus stimulation influenced the idioventricular electrocardiogram in these instances either because it altered the location of the idioventricular pace-maker or produced bundle-branch block.

Whether or not vagus stimulation may alter the form of the ventricular complexes when the ventricles are responding to supraventricular stimuli has been much discussed. In 1909, Hering[8] recorded abnormal ventricular complexes during vagus stimulation in a dog; and each ventricular beat was preceded by an auricular beat, as shown by the electrocardiogram and the suspension curve. Hering was of the opinion that these ventricular beats were supraventricular in origin, an interpretation which has been questioned by others.[9] If Hering's view is the correct one, we must assume a bundle-branch block to account for the form of the ventricular complexes. A similar assumption would be necessary to explain the abnormal ventricular complexes obtained by Kraus and Nicolai[7] by stimulating the auricles during complete vagus inhibition.

Rothberger and Winterberg[10] found that stimulation of either accelerator nerve during vagus inhibition almost always gave rise to rhythmic and typically diphasic ventricular complexes. In some of their figures[10] (Fig. 1c p. 466) each abnormal ventricular complex is preceded by an auricular contraction. It seems to us possible that in these instances the abnormal ventricular beats were responses to supraventricular stimuli. If this be true we would again be dealing with an abnormal spread of a supraventricular stimulus over the ventricles as a result of nervous influences. The effect of vagus stimulation was complicated in these experiments, however, by the effect of accelerator stimulation, and, moreover, the type of ventricular complex depended on which accelerator was stimulated, so that conclusions as to the relationship of the vagi to the abnormal complexes are difficult to draw. A summary of the experimental evidence shows that although it is possible that vagus stimulation produced bundle-branch block in animals in certain instances, unquestionable examples of this phenomenon are lacking.

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8. Hering, H. E.: Experimentelle Studien am Saügetieren über das Elektrokardiogramm, Arch. f. d. ges. Physiol., 1909, cxxvii, 155.

9. Kahn, R. H.: Das Elektrokardiogramm, Ergebn. d. Physiol., 1914, xiv, 1. Samojloff, A.: Weitere Beiträge zur Elektrophysiologie des Herzens, Arch. f. d. ges. Physiol., 1910, cxxxv, 417. Rothberger, J., and Winterberg, H.: Ueber die Beziehung der Herznerven zur Form des Elektrokardiogramms, Arch. f. d. ges. Physiol., 1910, cxxxv, 506.

10. Rothberger, J., and Winterberg, H.: Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachycardie durch Acceleransreizung, Arch. f. d. ges. Physiol., 1911, cxlii, 461.

So far as we know, no clinical case has as yet been reported in which stimulation of the vagus produced diphasic ventricular complexes. In the following case vagus stimulation produced such complexes although the ventricles were responding to supraventricular stimuli. The case also presents other unusual features. The history and examination of the patient have been recorded in another place[11] (Case 2).

BUNDLE-BRANCH BLOCK PRODUCED BY VAGUS STIMULATION

This patient showed at times no less than four separate and distinct rhythms. Rhythm 1, the normal rhythm, is illustrated in Figures 1, 2 and 3. The electrocardiograms have a normal outline in Leads 1 and 2, while in Lead 3 the QRS group of the ventricular complex is one of those bizarre forms occasionally recorded in this lead even in people with normal hearts.[12] T is partially inverted in Lead 3. The P-R interval of the normal rhythm is about 0.17 second and the a-c interval about 0.20 second.

The second rhythm observed, which may be called Rhythm 2, is illustrated in Figures 4, 5 and 6. Both the auricular and the ventricular complexes are abnormal. P is upright in Lead 1 and inverted in Leads 2 and 3. The P-R interval is reduced to about 0.10 second and the a-c interval to about 0.15 second. The reduction of the As-Vs interval with the inversion of P in Leads 2 and 3 indicates that the site of origin of this rhythm was in the neighborhood of the A-V node. The fact that the P-R interval is only slightly reduced means that the pace-maker was in the upper part of this region.

The ventricular complexes of Rhythm 2 are abnormal in all leads. In contrast to those of the normal rhythm they exhibit the following characteristics: they are typically diphasic rather than polyphasic. The initial deflection is of greater amplitude and of longer duration, its duration being 0.10 second or more. The final deflection extends in the opposite direction from the initial deflection in all leads and is exaggerated especially in Leads 2 and 3. These characteristics indicate that the abnormality of the ventricular complexes of Rhythm 2 is due to bundle-branch block. The fact that the initial deflection is upright in Lead 1 and inverted in Lead 3 indicates that the right branch of the His bundle is the one affected. Rhythm 2 may therefore be described as an atrioventricular rhythm with right bundle-branch block.

The relationship between the normal rhythm and Rhythm 2 was as follows. During the first few days that the patient was under

11. Wilson, Frank N.: Three Cases Showing Changes in the Location of the Cardiac Pace-Maker, Associated with Respiration, THE ARCHIVES INT. MED., 1915, xvi, 86.

12. Lewis, T.: Clinical Electrocardiography, London, 1912.

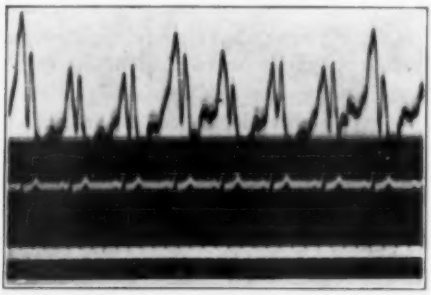

Fig. 1.—In this, as in the figures which follow, an ordinate of 1 cm. is equal to 1 millivolt. Rhythm 1, Lead 1. P-R interval, 0.17 second; a-c interval, 0.20 second. Duration of QRS group, 0.08 second. Heart rate 75.

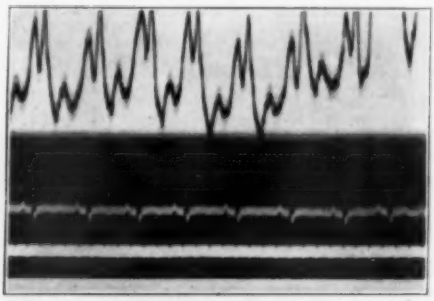

Fig. 2.—Rhythm 1, Lead 2. The P-R and a-c intervals are the same as in the previous figure. Duration of QRS group, 0.08 second. Heart rate 75.

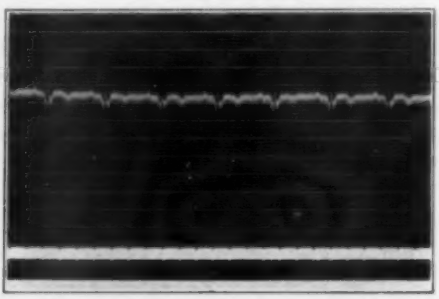

Fig. 3.—Rhythm 1, Lead 3. The P-R interval is the same as in Figure 1. Duration of QRS group, 0.10 second. The QRS group is bizarre and T is partially inverted.

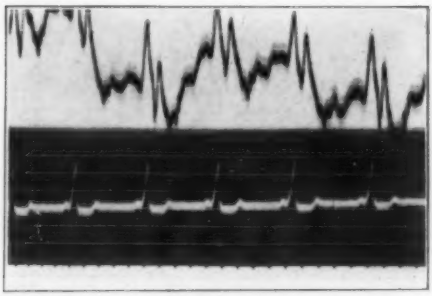

Fig. 4.—Rhythm 2, Lead 1. P-R interval, 0.10 second, a-c interval 0.15 second. Duration of QRS group, 0.10 second. The amplitude of R′ is greater than that of R in Figure 1. T is inverted. P is upright. Heart rate 66.

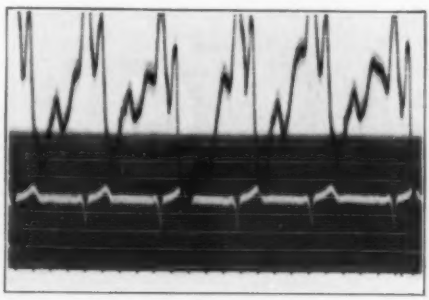

Fig. 5.—Rhythm 2, Lead 2. The P-R and a-c intervals are the same as in Figure 4. Duration of QRS group, 0.10 second. The ventricular complex is diphasic and T is exaggerated. P is inverted. Heart rate 62.

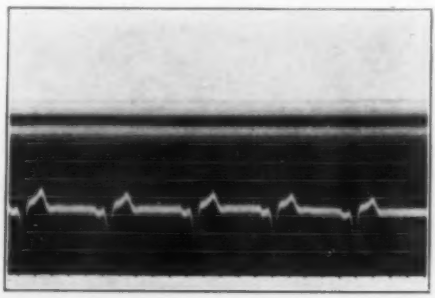

Fig. 6.—Rhythm 2, Lead 3. The P-R interval is the same as in Figure 4. Duration of QRS group, 0.13 second. The amplitude of the initial deflection is greater than that of the initial deflection of the ventricular complexes in Figure 3. T is exaggerated. P is inverted. Heart rate 62.

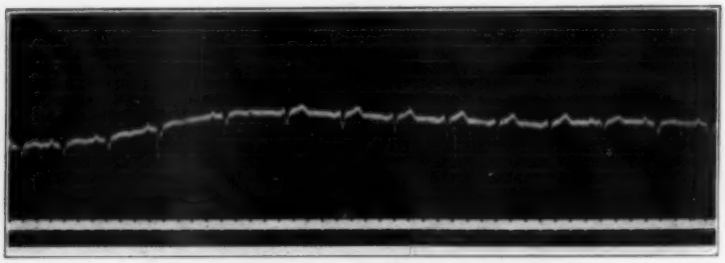

Fig. 7.—Lead 2. Rhythm 1 converted into Rhythm 2 by moderately deep respiration. Note the transitional ventricular complex at the end of the abnormal rhythm.

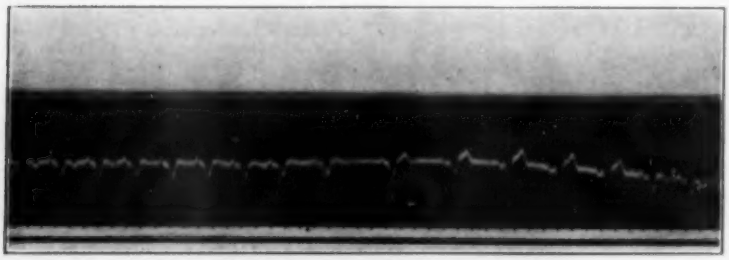

Fig. 8.—Lead 3. Rhythm 1 converted into Rhythm 2 by deep respiration. At the beginning of the abnormal rhythm the change in the form of P is sudden while the change in the form of the ventricular complex is gradual.

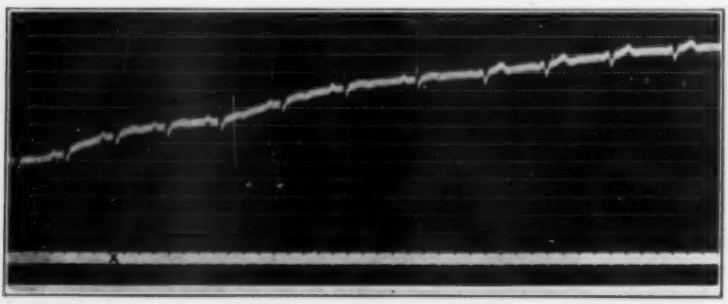

Fig. 9.—Lead 2, Rhythm 1 converted into Rhythm 2 by pressure on the right vagus. Pressure was begun at x and continued until the abnormal rhythm appeared.

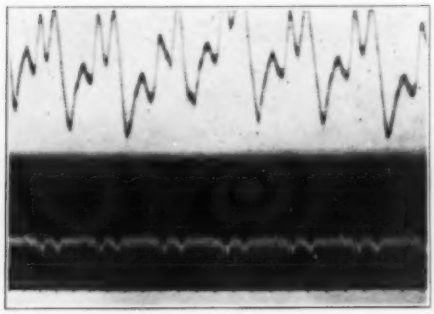

Fig. 10.—Rhythm 1, Lead 3. Taken at the end of an atropin experiment. Rhythm 2 was constantly present before the atropin was given.

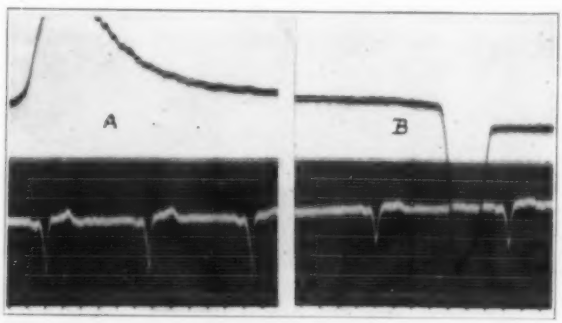

Fig. 11.—Rhythm 2, Lead 3. Rhythm 2 slowed by right vagus pressure; A, beginning, and B end of a period of right vagus pressure lasting eleven seconds.

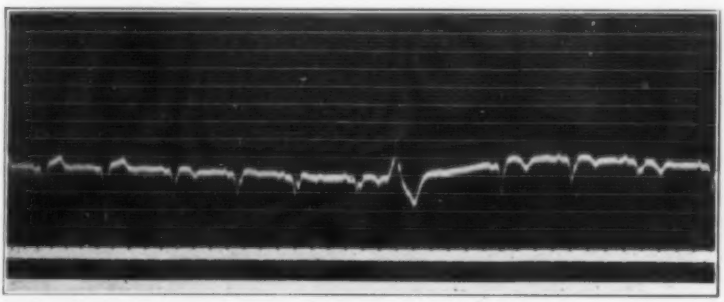

Fig. 12.—Lead 3. The first part of the figure shows a gradual transition from Rhythm 2 to Rhythm 1. This transition took place spontaneously. The P complex of the third cycle is transitional between those that precede and those that follow it. A ventricular extrasystole occurs.

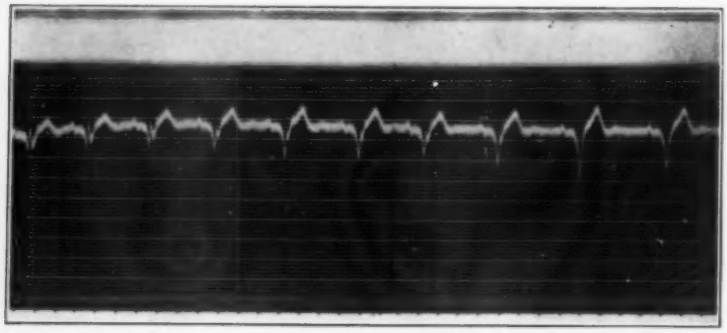

Fig. 13.—Lead 3. P is upright throughout the figure and the P-R interval is that of Rhythm 1. There is a gradual transition from complexes of the normal type to those characteristic of right branch block. Note the disappearance of the upright spike of the normal ventricular complex during the transition.

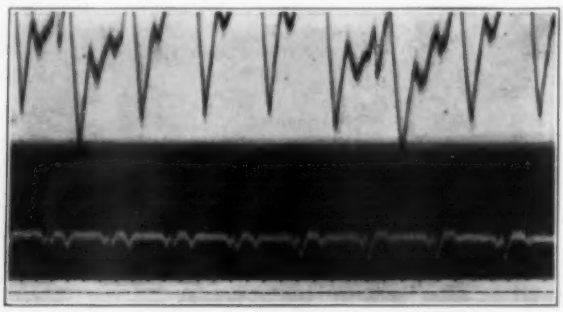

Fig. 14.—Lead 3. P is inverted and the P-R interval is reduced. The first four ventricular complexes are of the normal type. The last four ventricular complexes are diphasic and are of the type associated with Rhythm 2 except that their amplitude is much less. This curve was taken during an atropin experiment. The last four ventricular complexes probably represent incomplete branch block.

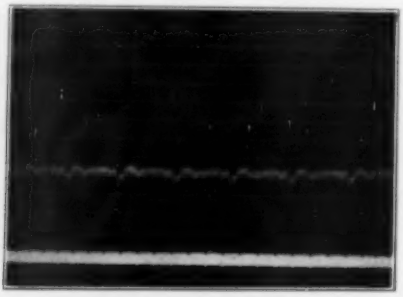

Fig. 15.—Lead 3. The inverted auricular complexes of Rhythm 2 are associated with the ventricular complexes of Rhythm 1.

observation, the normal rhythm was the one usually present. At this time Rhythm 2 could be produced almost at will by having the patient take a deep breath (Figs. 7 and 8). The abnormal rhythm appeared shortly after the beginning of expiratory slowing and after persisting for a number of beats disappeared as the heart rate quickened. The normal rhythm could also be converted into the abnormal rhythm by pressure upon the vagus nerves (Fig. 9). No difference between the two vagi was noted. Although, when the first electrocardiograms were taken, Rhythm 2 disappeared shortly after it was produced by deep breathing or vagal pressure, as time went on it showed a greater and greater tendency to persist, and at the end of the first week of the examination it was the rhythm usually present. At this time the normal rhythm could be produced by having the patient take a rapid succession of deep breaths. It was also possible to convert Rhythm 2 into the normal rhythm by the subcutaneous administration of 1/50 grain of atropin (Fig. 10) and this was done on five different occasions. After the normal rhythm had been produced by atropin it was impossible to cause Rhythm 2 to return by forced respiration or by any other means used to produce it before it appeared spontaneously.

Rhythm 2 could be slowed considerably by vagus stimulation (Fig. 11) the right vagus being somewhat more effective than the left. This shows that in this patient the upper portion of the junctional tissues was under vagus control.

To sum up; the normal rhythm when spontaneously present could be converted into an atrioventricular rhythm with right branch-bundle block by indirect or direct stimulation of the vagus nerves, and the abnormal rhythm when spontaneously present could be converted into the normal rhythm by the administration of atropin in doses sufficient to paralyze the vagi. This group of facts can lead to but one conclusion and that is that the vagi were partially responsible both for the change in the location of the pace-maker and for the abnormality of the ventricular complexes. The relationship of these nerves to the former has been discussed elsewhere[11] (Case 2).

Before discussing the effect of the vagus on the form of the ventricular complexes, it is necessary to examine the relationship between the A-V rhythm and the bundle-branch block. The fact that both are so constantly associated in the present case might lead one to suspect that the abnormal location of the pace-maker was entirely responsible for the abnormality of the ventricular complexes. It is difficult to see how this could be possible, for as has been pointed out above, the pace-maker must have been situated high up in the junctional tissues above the division of the His bundle. Even in complete heart block, when the pace-maker is much lower and nearer to the bifurcation of the A-V

bundle, the ventricular complexes are normal. Furthermore, in the present case, although the change in the location of the pace-maker was an abrupt one the change in the form of the ventricular electrocardiogram was often very gradual (Fig. 8). Transitional P waves were sometimes seen at the onset or offset of the A-V rhythm (Fig. 12) but these were due not to a gradual change in the location of the pace-maker but to interference between two contraction waves, one beginning at the sinus and the other at the A-V node.[11] That the abnormality of the ventricular complexes did not depend on the presence of A-V rhythm is also demonstrated by the fact that transitions between the normal and the abnormal complexes sometimes occurred without the pace-maker leaving the sinus node (Fig. 13). At other times, on the other hand, an A-V rhythm of the same type as that of Rhythm 2 was associated with ventricular complexes of the

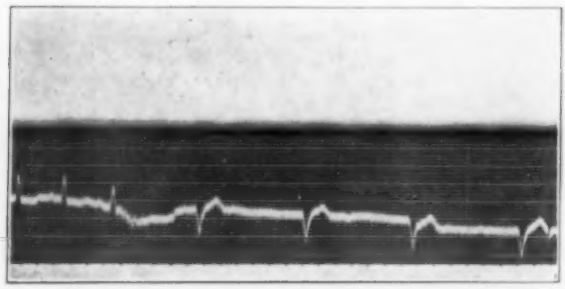

Fig. 16.—Lead 1. This curve illustrates the production of diphasic ventricular complexes in a second patient (see text). P cannot be seen during the abnormal rhythm.

normal type (Figs. 14 and 15). It would seem therefore that the bundle-branch block of Rhythm 2 did not depend on the abnormal site of impulse formation but that both were coordinated effects of vagus influence.

It is of course improbable that the bundle-branch block was due to vagus influence alone for it is rarely possible to produce diphasic ventricular complexes by vagus stimulation. We have carried out this procedure in a considerable number of patients and we have been able to produce such complexes in but one other instance (Fig. 16). The unsatisfactory character of the records obtained in that instance made it impossible to tell whether or not the ventricles were responding to supraventricular stimuli. It is probable therefore that in the previous patient, conduction through the right branch of the A-V bundle was already impaired and that this rendered it especially susceptible to vagus influence.

INCOMPLETE BUNDLE-BRANCH BLOCK

The characteristics of the abnormal ventricular complexes produced by the complete interruption of conduction through one branch of the A-V bundle are fairly well known both from experimental and clinical observations. Very little is known, however, about the ventricular complexes of incomplete block in one of the branches of the A-V bundle. For this reason, gradual transitions between normal ventricular complexes and those of bundle-branch block are of par-

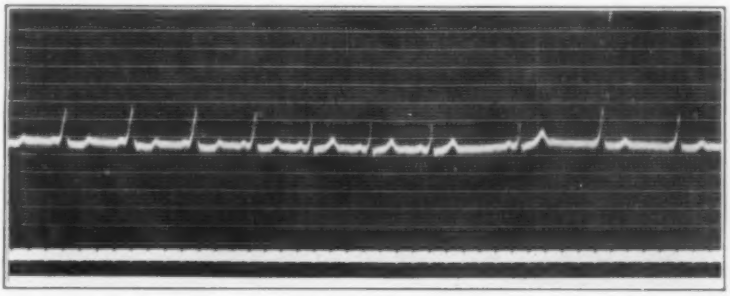

Fig. 17.—Lead 1. A spontaneous transition from Rhythm 2 to Rhythm 1 and the return to Rhythm 2. The transitions are sudden.

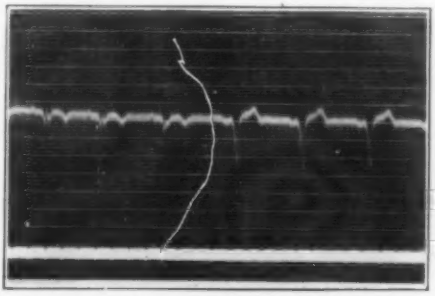

Fig. 18.—Lead 3. A sudden transition from Rhythm 1 to Rhythm 2.

ticular interest for presumably they represent varying degrees of partial bundle-branch block and their analysis may aid in the recognition of this condition when transitions are absent. In the present case, some of the transitions from the normal to the abnormal complexes were sudden (Figs. 17 and 18); but as a rule they were gradual. For the purpose of determining the characteristics of the ventricular complexes of partial bundle-branch block spontaneous transitions should be chosen

in order to eliminate the effects of the respiratory changes in the position of the heart on the ventricular complex. Such spontaneous transitions from normal to abnormal and from abnormal to normal complexes are shown in Figures 12 and 13. From the analysis of a large number of such transitions it was found that changes in the QRS group and in T usually appeared simultaneously. The most constant feature of the transitional complexes was their diphasic character, which was usually evident even in those nearest the normal complexes, and this change is probably present in the lightest grade of block. On the other side, the transitional complexes differed from the fully developed abnormal complexes principally in their lesser amplitude. As one proceeds from the abnormal complexes to those typical of complete branch-bundle block the amplitudes of the QRS group and of T gradually increase, and as these two deflections are in opposite directions the diphasic character of the complexes is gradually accentuated (Figs. 8 and 13). Although an increase in the duration of the initial deflection usually appeared with the first of the abnormal complexes it was usually much less striking than their diphasic character. The disappearance of the upright spike of the QRS group of the normal ventricular complex in Lead 3 during the transitions is interesting (Figs. 8 and 13).

VENTRICULAR COMPLEXES SUGGESTING LEFT BUNDLE-BRANCH BLOCK AT THE BEGINNING OF ATROPIN EXPERIMENTS AND DURING PAROXYSMS OF TACHYCARDIA

The effect of atropin on Rhythm 2 was complicated by a new rhythm which usually appeared about eight minutes after the injection of 1/50 grain of atropin sulphate and recurred with frequent transitions to the normal rhythm for from three to five minutes. This third rhythm is illustrated in Figures 19 (Lead 1) and in 20 (Lead 3). Although no P waves are seen in the electrocardiogram, it is evident from the tall venous waves which occurred during this rhythm (Fig. 21) that auricles and ventricles contracted simultaneously. This indicates that the site of origin of Rhythm 3 was in the lower junctional tissues. The change in the location of the pace-maker from the upper (Rhythm 2) to the lower (Rhythm 3) junctional tissues after atropin is probably analogous to the appearance of A-V rhythm in normal individuals under similar conditions.[13] The transitions between Rhythm 1 and Rhythm 3 differed from those between Rhythm 1 and Rhythm 2 in that they were usually sudden (Figs. 19, 20 and 22). Ventricular complexes which may be regarded as transitional in form

13. Wilson, Frank N.: THE ARCHIVES INT. MED., page 989, this issue.

between the ventricular complexes of the normal rhythm and those of Rhythm 3 were frequently recorded, however, and these usually occurred during a period just preceding the appearance of Rhythm 3. These transitional complexes (Fig. 23) appeared only after atropin and were not associated with any change in the location of the pacemaker as is shown by the length of the P-R interval and the form of the P waves which precede them (Fig. 23). It seems likely, therefore, that in Rhythm 3 as in Rhythm 2 the abnormality of the ventricular complexes did not depend on the abnormal site of impulse formation.

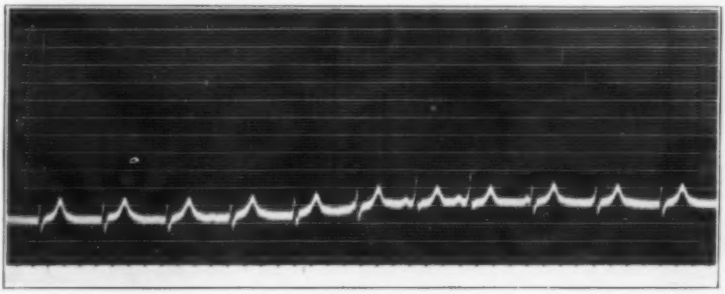

Fig. 19.—Rhythm 3, Lead 1. The ventricular complexes are not diphasic but T is exaggerated. A transition from Rhythm 3 to Rhythm 1 occurs. P cannot be identified during Rhythm 3.

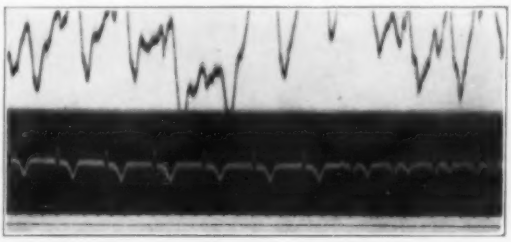

Fig. 20.—Lead 3. A transition from Rhythm 3 to Rhythm 1 is shown. P is not visible during Rhythm 3.

Transitions between a sinus rhythm and Rhythm 3 are illustrated in Figures 19 and 22. The P wave gradually approaches the ventricular complex and finally disappears within it. The reverse process occurs when the abnormal gives place to the normal rhythm (Figs. 20 and 22). The fact that the P waves remain normal during the transitions indicates that the auricular contractions which they represent were responses to the sinus node. The shortening of the P-R interval indicates, therefore, that a lower center has escaped and that

the ventricles are responding to this center. After several heart cycles the higher rate of this lower center enabled it to replace the sinus node as pace-maker for the auricles also. The reverse process took place when the inherent rate of the sinus became more rapid than that of the ectopic center. When transitions occurred between Rhythm 2 and Rhythm 3 a similar phenomenon took place. The inverted P of Rhythm 2 gradually approached and disappeared into the ventricular

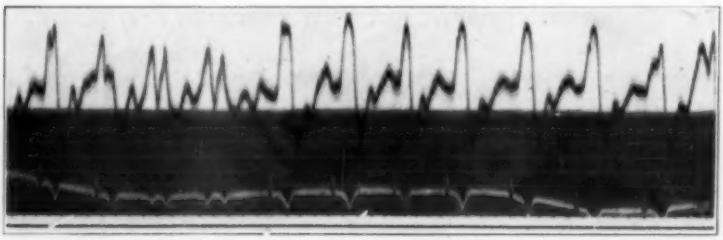

Fig. 21.—Lead 3. A transition from Rhythm 1 to Rhythm 3 occurs in the last part of the figure. The venous pulse during Rhythm 3 is dominated by a tall wave such as is usually seen when auricles and ventricles contract simultaneously. This wave is no broader that the *a* wave which occurs during the normal rhythm (Cycles 3 and 4). Note that even when P only just emerges from the ventricular complex in the second cycle from the right hand side of the figure *a* and *c* are separately indicated in the venous pulse.

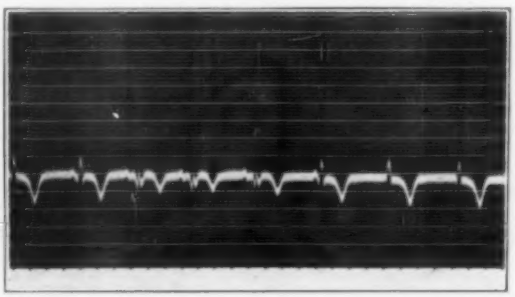

Fig. 22.—Lead 3. A transition from Rhythm 3 to sinus rhythm occurs and also a transition in the reverse direction. Notice that P moves out of the ventricular complex at the end of Rhythm 3 and reenters the ventricular complex when Rhythm 3 reappears.

complex. The period of transition lasted for only one or two complexes, however, because of the close proximity of the two opposing centers (Fig. 24). The fact that P never emerged between R and T indicates that the impulses from the center which was responsible for Rhythm 3 must have reached the auricles at some time during the R wave, or in other words that these impulses arose from the region of

the A-V node itself. The tall venous waves of Figure 21 also indicate that during Rhythm 3 auricular systole fell during the first portion of ventricular contraction.

The ventricular complexes of Rhythm 3 are distinctly abnormal. In Lead 3 (Fig. 24) they are typically diphasic. The duration of the initial deflection is not distinctly lengthened but its amplitude is increased and T is exaggerated. In Lead 1 (Fig. 19) the ventricular

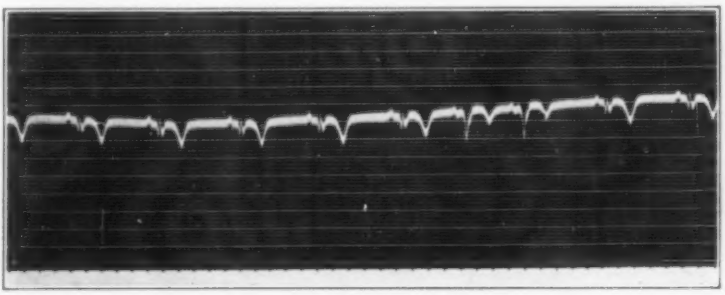

Fig. 23. Lead 3. Taken during an atropin experiment. The ventricular complexes of the first part of the figure are transitional between those of the normal type and those seen in Rhythm 3. Two ventricular complexes transitional in form between the ventricular complexes in the first part of this figure and the ventricular complexes of Rhythm 2 occur in the latter part of the curve.

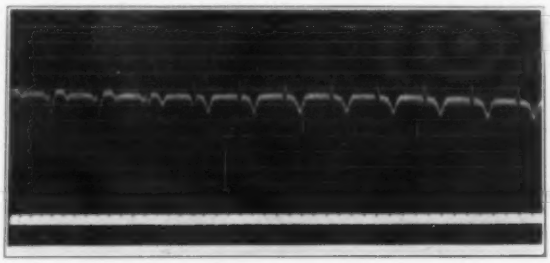

Fig. 24.—Lead 3. A transition from Rhythm 2 to Rhythm 3 occurs. The inverted P wave enters the ventricular complex at the beginning of Rhythm 3. The period of transition is short.

complexes are not diphasic. When compared with the normal, however, R is shorter while S and T are exaggerated. Before discussing the question of the significance of these abnormal complexes let us examine a fourth rhythm observed in this patient.

This patient had at times paroxysms of tachycardia which always began and ended suddenly. During the six weeks that he was under observation two such attacks were recorded. The rhythm present at

these times is illustrated in Figures 25, 26 and 27. Both attacks were stopped by Valsalva experiments and the end of one of them is shown in Figure 28. In this figure it will be seen that the abnormal rhythm ceased abruptly and after a long postparoxysmal pause the sinus rhythm returned. The rate of the heart during the paroxysm was about 170. In contrast to most patients who are subject to attacks of paroxysmal tachycardia our patient exhibited very few single extrasystoles; only two (Figs. 12 and 28) were recorded in a large number of tracings and these being of the ventricular type bore no relationship to the attacks of tachycardia.

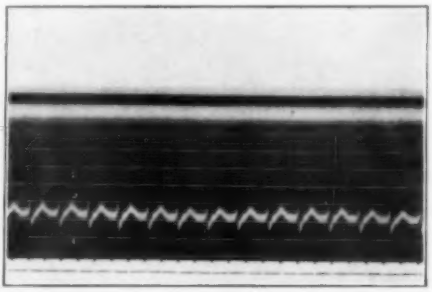

Fig. 25.—Rhythm 4, Lead 1. The ventricular complexes are like those in Figure 20. P is not seen.

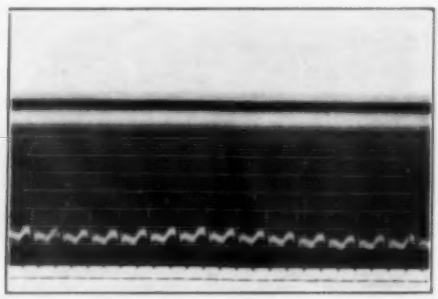

Fig. 26.—Rhythm 4, Lead 2. The ventricular complexes are diphasic. P is not seen. The heart rate is 170.

The electrocardiograms taken during the attacks show no definite P waves and except for the difference in heart rate resemble very closely those obtained during Rhythm 3. The venous pulse is of the positive type usually seen in paroxysmal tachycardia (Fig. 27). Such a phenomenon may be due either to the fact that the auricular contractions fall on the ventricular contractions of the prevoius heart cycle

or it may be due to the fact that both chambers are stimulated simultaneously from a pace-maker in the junctional tissues. There are two reasons for thinking that the latter explanation is the correct one in the present case. The first is the marked similarity between the electrocardiograms of Rhythms 3 and 4. This close resemblance between the electrocardiograms of the two rhythms makes it seem likely that they originated at the same point. The second reason for thinking

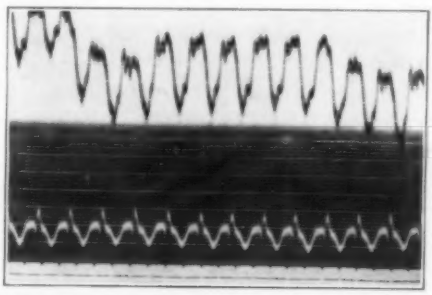

Fig. 27.—Rhythm 4, Lead 3. The ventricular complexes are typically diphasic and like those of Rhythm 3 in this lead. P is not seen.

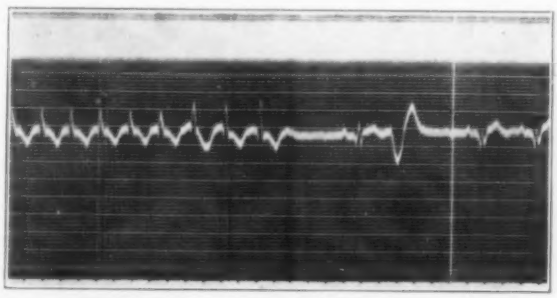

Fig. 28.—The end of an attack of paroxysmal tachycardia is shown. There is a long postparoxysmal pause followed by a normal contraction and then an extrasystole. The last ventricular complex of the paroxysm does not differ from the preceding ones.

that Rhythm 4 arose in the junctional tissues is that the last ventricular complex of the paroxysm does not differ from the rest (Fig. 28). This is not the case when auricular contraction falls on the ventricular contraction of the previous heart cycle; for when this occurs the last ventricular complex of the paroxysm, unlike the others is not modified by a simultaneous P. Paroxysmal tachycardia originating within the

junctional tissues is comparatively rare. Cases have been studied electrocardiographically by Lewis[14] and by Cohn.[15]

The abnormal ventricular complexes of Rhythms 3 and 4 may have been due to an abnormal spread of the contraction wave over the ventricles because of a block in the conduction system. These complexes strongly suggest a block in the left branch of the His bundle but they are not perfectly typical. This discrepancy may be explained by assuming that the block was a partial one affecting the left branch itself or a complete one affecting one of the divisions of this structure.

Rothberger and Winterberg[9] have shown that the accelerator nerves when stimulated separately may profoundly change the contour of the ventricular complexes even when these are responses to supraventricular stimuli. These investigators have obtained complexes of somewhat the same outline as those of Rhythms 3 and 4 by stimulation of the accelerator but we regard it as improbable that the abnormal complexes of these rhythms were due to abnormal activity of this nerve.

In the present case therefore the ventricular complexes were at times normal, at times typical of right bundle-branch block, and at still other times suggestive of left bundle-branch block. It does not seem to us that a complete explanation can be offered for all the changes observed but it should be pointed out that a similar condition of affairs has been observed both in man and in experimental animals. We have already referred to the clinical case described by Mathewson[4] in which an irregular alternation of ventricular complexes of right and left branch block with complexes of the normal type occurred. A similar heart mechanism can be produced in animals by ligation of the septal artery (Kahn[9]). The variations in the ventricular complexes in the present case differ from similar variations previously observed, however, in that they were, in a great measure at least, produced by changes in vagus influence.

SUMMARY

The case here reported showed at different times four distinct rhythms and at least three types of ventricular complexes.

In the first rhythm the ventricular complexes were normal and the pace-maker was in the normal location.

In the second rhythm the ventricular complexes were characteristic of a block in the right branch of the His bundle. These abnormal

14. Lewis, T.: Auricular Fibrillation and its Relationship to Clinical Irregularity of the Heart, Heart, 1909-1910, i, 306; Paroxysmal Tachycardia, Accompanied by the Ventricular Form of Venous Pulse, Heart, 1910-1911, ii, 127.

15. Cohn, A. E.: A Case of Paroxysmal Tachycardia, Heart, 1910-1911, ii, 170.

ventricular complexes were usually but not always associated with an atrioventricular rhythm originating in the upper levels of the junctional tissues. Both the A-V rhythm and the abnormal ventricular complexes could be produced by vagus stimulation and when spontaneously present could be abolished in favor of the normal rhythm by the administration of atropin.

Ventricular complexes, transitional in form between the normal complexes and the abnormal complexes mentioned above are discussed.

Rhythm 3 appeared during the early stages of atropin action and at no other time. The ventricular complexes of this rhythm were abnormal and suggested a block in the left branch of the His bundle. The pace-maker was situated in the region of the A-V node. Ventricular complexes transitional in form between those of the normal rhythm and those of Rhythm 3, occurred, however, while the pace-maker was situated at the sinus node. It is probable therefore that the abnormality of the ventricular complexes of Rhythm 3 did not depend on the abnormal site of origin of this rhythm.

Rhythm 4 was a paroxysmal tachycardia which originated at the same point as Rhythm 3 and which was associated with the same type of ventricular complex.

The various changes in the mechanisms of the heart beat observed in this case occurred, in a great measure at least, in response to changes in vagus control.

Although the changes in the form of the ventricular complex were usually associated with a change in the location of the site of impulse formation, this was not invariably the case, so that it is likely that both these changes were coordinated effects of variations in vagus influence.

OIDIOMYCOSIS IN CALIFORNIA, WITH ESPECIAL REFERENCE TO COCCIDIOIDAL GRANULOMA

INCLUDING NINE NEW CASES OF COCCIDIOIDAL GRANULOMA AND ONE OF SYSTEMIC BLASTOMYCOSIS *

ERNEST C. DICKSON, M.D.
SAN FRANCISCO

A discussion of that form of oidiomycosis which is known as coccidioidal granuloma would seem to be appropriate at this congress, since it is a disease which is apparently confined to the American continents. The first reported case was observed by Posadas[1] in Buenos Aires, and was described by that author and by Wernike.[2] The remaining thirty-nine cases have been observed in North America, the majority in California, and of the latter the greater number seem to have acquired the disease in the San Joaquin Valley. The first case which was recognized in California was reported by Rixford[3] in 1894, and, together with a case which was observed in the same year by Thorne[4] and Robinson, was later described in detail by Rixford and Gilchrist.[5] Posadas and Wernike, as well as Rixford and Gilchrist, believed that the infecting organism was a protozoan belonging to the group of *Coccidia*, and on that account the latter authors suggested the name of *Coccidioides immitis*. In 1900 another case was observed by Ophüls and Moffit,[6] who found that the parasite grew readily on artificial mediums, and that it developed as a mold which apparently belonged to the group of *Oidia*. Ophüls[7] then suggested the names *Oidium coccidioides* for the parasitic organism and coccidioidal granuloma for the lesions which it produces.

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* From the Divisions of Pathology and Medicine of Leland Stanford Junior University, School of Medicine.

* Read before the Seventh Pan-American Medical Congress, June 19, 1915.

1. Posadas: Psorospermiose Infectante Generalisee, Rev. de Chir., 1900, xxi, 277.

2. Wernike: Ueber einen Protozoandefund bei Mycosis fungoides, Centralbl. f. Bakteriol., 1892, xii, 859.

3. Rixford: Case Demonstration, Occid. Med. Times, 1894, viii, 326.

4. Thorne, W. S.: A Case of Protozoic Skin Disease, Occid. Med. Times, 1894, viii, 703.

5. Rixford and Gilchrist: Two Cases of Protozoan (Coccidioidal) Infection of the Skin and Other Organs, Johns Hopkins Hosp. Rep., i, 211.

6. Ophüls and Moffitt: A New Pathogenic Mould, Philadelphia Med. Jour., 1900, v, 1471.

7. Ophüls: Further Observations on a Pathogenic Mold Formerly Described as a Protozoan, Jour. Exper. Med., 1905, vi, 443.

In July, 1914, MacNeal and Taylor[8] collected the reports of twenty-four cases which had been recorded in the literature before March of the same year, but they overlooked one case which had been reported by Evans[9] in 1909 and another which had been reported by Chipman[10] in 1913. Since the publication of their report, Roblee[11] has reported one case, Cooke[12] has reported two, and Brown and Cummins[13] have reported two, so that in all there have been thirty-one established cases recorded in the literature. In the Pathological and Bacteriological Laboratories of Leland Stanford Junior University, School of Medicine (formerly Cooper Medical College), sixteen cases of coccidioidal granuloma have been studied. Six of these have been reported by Ophüls,[14] one by Bowles[15] and one by Chipman,[10] but there still remain eight hitherto unrecorded cases, four of which were studied by Ophüls and four by Ophüls and myself, which form the basis of the present report. In addition to these, there is one more case which was observed by S. J. Gardner and H. W. Gibbons, to whom I am indebted for the clinical and pathologic records.

The origin of the infecting organism is unknown, but it is of considerable interest that of the forty known patients, thirty-five had been residents of California, and three had visited the state. Twenty-seven of the patients had been residents of or had spent some time in the San Joaquin Valley, and of the eight other persons who developed the disease in California, there are but two of whom there is record that they had not been in the San Joaquin Valley.

The majority of cases have occurred in laboring men. Thirty-seven were in adult males, one in a male child about 3 years of age, and two were in women. There is no apparent racial susceptibility, since persons of various nationalities have been affected.

The mode of onset varies in different cases, the most striking feature being the remarkably close resemblance to tuberculosis which

8. MacNeal and Taylor: Coccidioides Immitis and Coccidioidal Granuloma, Jour. Med. Research, 1914, xxx, 261.

9. Evans: Coccidioidal Granuloma and Blastomycosis in the Central Nervous System, Jour. Infect. Dis., 1909, vi, 523.

10. Chipman, E. D.: The Newer Cutaneous Mycoses, Jour. Amer. Med. Assn., 1913, lxi, 407.

11. Roblee: Report of a Case of Oidiomycosis, California State Jour. Med., 1914, xii, 390.

12. Cooke, J. V.: Immunity Tests in Coccidioidal Granuloma, THE ARCHIVES INT. MED., 1915, xv, 479.

13. Brown, P. K., and Cummins, W. T.: A Differential Study of Coccidioidal Granuloma and Blastomycosis, THE ARCHIVES INT. MED., 1915, xv, 608.

14. Ophüls, William: Coccidioidal Granuloma, Jour. Am. Med. Assn., 1905, xlv, 1291.

15. Bowles, F. H.: Coccidioidal Granuloma, Jour. Am. Med. Assn., 1912, lix, 2253.

is evident in the initial lesions as well as in the clinical course and in the pathologic picture. In a considerable number of the reported cases, the initial lesions occurred in the skin as nodular, granulomatous areas in the corium which usually ulcerated and gradually increased in size. In the majority of the remaining cases, the initial symptoms indicated primary pulmonary infection, and strongly suggested pulmonary tuberculosis; but in a few cases the first lesions occurred in the joints, and in at least three of our series of cases a diagnosis of tuberculosis of the joints had been made. It is a point of considerable interest that in two of our cases the joint lesions developed immediately after trauma.

The primary skin lesions usually appear as small, indurated nodules which may be quite painless, but which gradually enlarge and finally show small collections of pus on the surface. After ulceration occurs, a dirty crust forms, and the lesion slowly increases in size by extension at the edges. Beneath the crust is a ragged, nodular, granulomatous surface which shows numerous small accumulations of pus, and from which often a large amount of pus can be squeezed. Usually there is fairly early involvement of the regional lymph nodes which may or may not be painful. The appearance of the skin lesions so closely resembles the more acute forms of cutaneous tuberculosis in the gross and in microscopic sections that diagnosis can be made only by the identification of the characteristic spherical bodies in the pus or in the tissues, or in the cultivation of the fungus. The lesions may remain localized in the skin for a considerable length of time, in Posada's case seven years and in Rixford's first case nine years; but, with one exception, in all of the reported cases in which they first appeared in the skin, a general infection eventually occurred.

When the initial infection occurs in the respiratory tract, the clinical picture is that of pulmonary tuberculosis. The patients usually complain of cough, weakness, loss of weight, gastro-intestinal disturbances, fever and night sweats. There is frequently blood-stained sputum in which, however, no tubercle bacilli can be found. There is recorded but one exception to the latter characteristic. In the case reported by Chipman,[10] the diagnosis of coccidioidal granuloma was established by microscopic examination of tissue from a lesion of the skin, but tubercle bacilli were found in the sputum on at least two occasions by different observers. It is unfortunate that necropsy was not permitted in this case. Physical examination shows all the signs of pulmonary involvement, and pleural effusion is often found. Unless one thinks to examine the fresh sputum for the spherical bodies of coccidioidal granuloma, a diagnosis of pulmonary tuberculosis will almost surely

be made. In cases in which pulmonary lesions have occurred, the onset of the general infection rapidly ensues.

One case is reported by Carson and Cummins,[16] in which a diagnosis of tuberculous laryngitis was made a few months before the onset of the terminal general infection; but in this case complete necropsy was not permitted, and it was impossible to determine the nature of the lesion in the larynx.

When the infection first manifests itself in the joints, the picture is that of an acute or subacute arthritis, and, as stated before, it is interesting that in some of the cases the arthritis developed immediately after trauma to the parts affected. The joints are swollen, red and painful, and eventually become fluctuating. Roentgen-ray examination reveals a type of bone destruction which is indistinguishable from tuberculosis. If incision is made into the fluctuating mass, or if spontaneous rupture occurs, a large amount of creamy and sometimes blood-stained pus escapes, and even though the walls of the abscess and the bone be thoroughly curretted, the sinuses usually refuse to heal. In the joint cases, as in the skin cases, the regional lymph nodes soon become involved, but in the former there is the greatest hope of successful treatment, since the progress of the disease has been arrested in two cases which were treated by Gardner by early amputation of the foot and resection of the elbow joint, respectively.

The almost constant outcome of the disease is general infection with rapidly fatal termination. There are, in so far as is known to the author, only four cases in which a clinical diagnosis had been established which did not progress to a general infection. One of these patients (Case 39) is still living about two years after the appearance of the initial symptoms, but it is as yet too soon to say what the outcome will be, especially as there is still evidence of an active process in one knee. Another patient (Case 33), who was apparently cured, died of an intercurrent disease about two years after he seemed to be well; but as no necropsy was performed, it is impossible to say that complete recovery had taken place. The other two cases are those in which Gardner[17] performed early operation, and in these there was apparently a complete arrest of the process.

The symptoms of the patients with a general infection vary according to the distribution of the lesions in the body. In those cases in which there are no skin lesions, the clinical picture resembles that of miliary tuberculosis or of typhoid fever. When skin lesions are

16. Carson, G. R., and Cummins, W. T.: A Case of Coccidioidal Granuloma, Jour. Am. Med. Assn., 1913, lxi, 191.

17. Gardner, S. J.: An Unusual Infection in the Bones of the Foot, California State Jour. Med., 1904, ii, 386.

present, the condition often resembles malignant syphilis or glanders. In one case,[18] that which occurred in a child, the terminal symptoms were those of meningitis, and the patient was treated for cerebrospinal meningitis. It can be said, however, that usually there is extreme exhaustion, high fever, often of a septic type and accompanied by chills, frequent severe night sweats, progressive emaciation and anemia and a moderate leukocytosis. Quite frequently there is the formation of large, painless abscesses in the subcutaneous tissues which develop suddenly and usually burst and liberate large amounts of creamy pus. The sinuses which are so formed rarely close. Death usually occurs from exhaustion.

In the pathologic picture even more than in the clinical manifestations does this disease resemble tuberculosis. In several of the cases, the anatomic diagnosis at necropsy has been tuberculosis, and it was only when microscopic examination was made that the true nature of the condition was recognized. The individual lesions consist of typical tubercles with central caseation, multinuclear giant cells of the Langhans type, epithelioid cells and lymphocytes. In the lungs and in the abdominal organs and lymph glands there is usually marked caseation and comparatively little abscess formation, although in some of the tubercles one sometimes sees the small, central accumulations of leukocytes which are often seen in acute tuberculosis. When the bones and subcutaneous tissues are involved, there is much pus formation, and the contents of the abscesses are more truly pus than is the case in tuberculous abscesses, in that a fairly large number of true pus-cells are present. In the cases in which general infection has occurred, the usual picture is that of an acute, disseminated, miliary tuberculosis, and numerous tubercles are found in all parts of the body. It is not at all unusual to find a basilar meningitis which is indistinguishable from tuberculous meningitis, in which the distribution of the tubercles is confined to the basal meninges and to the folds of the meninges within the basal portions of the sulci. Evans[9] has pointed out that in this respect there is a distinct difference from blastomycotic involvement of the central nervous system, in which the lesions are found in the substance of the brain and of the cord.

A peculiar feature is the tendency to involve testicular tissue. This has been noted in a number of the human cases, but is much more noticeable in animals. If infection is produced in male animals by intraperitoneal injection, there is early involvement of the testicles which become swollen and hard and which soon suppurate and dis-

18. Ryfkogel, H. A. L.: Coccidioidal Meningitis, Jour. Am. Med. Assn., 1910, lv, 1730.

charge through sinuses. This phenomenon is as characteristic as in glanders, and affords early evidence of successful inoculation.

The parasitic organisms which cause the disease are easily found in the tissues, in the pus and in the sputum. They appear as spherical bodies about 30 microns in diameter with double-contoured capsules and a slightly granular protoplasm which is sometimes vacuolated. The capsule is highly refractile, and in some cases seems to have short knobs or prickles on the outer surface. A true nucleus has never been demonstrated. In the tissues these spherical bodies are found in the diseased areas in large numbers, usually within the tubercles, and frequently inside the multinuclear giant cells. In the walls of the abscess cavities and in the pus they are usually very numerous, and can be demonstrated with little difficulty. In the pus or in the sputum they are best seen in a fresh specimen prepared by placing a cover-slip over a drop of the material on a glass slide. If examination is made with but little light, the spherules stand out prominently and are easily distinguished from cells and from the myelin droplets which are also usually present. The bodies stain poorly with the ordinary staining methods, and are very apt to be overlooked in the stained smear.

Reproduction within the tissues occurs by a process of endosporulation, and the organism differs from the blastomyces in that true budding has never been observed. The spores develop by a division of the protoplasm within the capsule until a large number, a hundred or more, are formed, and when mature they are so closely packed together that they assume various shapes. They are released through a rupture in the capsule of the parent body, and it is not at all uncommon to find a number of the empty envelopes in a specimen of pus. The development of the adult forms from the spores has not been definitely traced because the spores are so small and they stain so poorly that it is impossible to follow the changes that occur after they escape from the parent body. However, Ophüls[7] was able to find a few cases in which the spores seemed to mature within the body of the parent before rupture of the capsule liberated them, and he believes that the adult forms develop directly from the spores by simple growth without further change than the formation of the relatively thick, double-contoured capsule.

On artificial culture mediums the organism develops as a white mold with short aerial hyphae in which chlamydospores develop. The transition from the spherical body that occurs in the tissues to the hyphae of the growth on the artificial culture mediums was first demonstrated by Ophüls[19] by studying cultures prepared by mixing the

19. Ophüls and Moffitt: A New Pathogenic Mold, Philadelphia Med. Jour., 1900, v, 1471. Ophüls: Further Observations on a Pathogenic Mold Formerly Described as a Protozoan, Jour. Exper. Med., 1905, vi, 443.

pus with the culture mediums in a hang-drop preparation. He found that if the spherical body was surrounded by even the smallest particle of tissue, no hyphae formation occurred, but that if it was free in the mediums, the hyphae developed by a process of outgrowth through the capsule. Sometimes but one hypha developed from a single sphere, but at other times there were several hyphae arising from different parts of the capsule. He was not able to find any evidence of endosporulation in the cultures.

Various attempts have been made to trace the development of the spherical bodies from the fungus form. Ophüls[7] found that if a fresh culture in which spore formation had not yet taken place was injected into susceptible animals no infection followed, but that if a spore-bearing culture was injected, practically all of the animals became infected. He concluded that the spherical bodies in the tissues must be derived in some way from the spores of the fungus, since in all cases there was rapid destruction of the hyphae that were injected. Wolbach[20] concluded from his experiments that the spherical bodies were developed directly from the mycelium, and that each sphere was derived from a single segment. MacNeal and Taylor[8] arrived at the same conclusion by a slightly different method of procedure, but it does not seem probable that the question is yet settled. Neither Wolbach nor MacNeal and Taylor mention having taken any precaution to make sure that they were injecting pure mycelia in which no spores were present. The presence of spores in some of the mycelial segments may readily explain why these particular segments survived when the great majority of those which were injected underwent rapid disintegration.

The only record of immunity tests in coccidioidal granuloma is that published by Cooke,[12] who made an exhaustive study of a case which was recently under observation at the University of California Hospital. In the summary of his report he says:

> In a case of coccidioidal granuloma studied, no specific complement-fixing bodies or agglutinins could be found in the blood serum. . . . No specific skin reaction could be demonstrated. Precipitins, however, could be demonstrated in the serum even when diluted 1:160, when an extract of dried cultures of the organism was used as precipitinogen. These precipitins were apparently specific.

There has been considerable difference of opinion as to the relationship which exists between coccidioidal granuloma and blastomycosis. European authors and a number of American authors from the Eastern and Middle Western States are inclined to believe that the

20. Wolbach: The Life Cycle of the Organism of Dermatitis Coccidioides, Jour. Med. Research, 1904, xiii, 53.

two conditions are practically identical. At least two of the cases of coccidioidal granuloma have been reported as blastomycosis,[21] although in one it was noted that it was an unusual type of blastomycosis in that reproduction occurred in the tissues by a process of endosporulation. Hyde[22] has suggested that the difference in the method of reproduction in the two conditions may be due to the fact that climatic conditions are different in the localities in which each is found. It is probable that he based his conclusion on the fact that in a case of blastomycosis in which the infection had become general, the patient completely recovered after removal to the southern part of California, for in relating the history of the case he says:

> If this result be due simply to climatic influence, it would seem to bear out the conclusions of those who have studied the phenomena of the disease, viz.: that the organisms are chiefly effective when developing in an environment favorable to their fructification.

That climate does not play so important a part in determining the character of the organism is shown by the fact that there have been a number of cases of true blastomycosis in California. In 1906, MacGowan[23] reported a case which he had observed in Southern California. In 1913, the author in collaboration with Dr. Harold P. Hill,[24] reported a case which had developed in the northern part of the state, and in the present report is the record of a case which developed in Michigan but which, after temporary improvement, progressed to a fatal termination in the San Joaquin Valley. In addition to these is an interesting series of cases which Dr. T. M. Williams of Palo Alto discussed before the California State Society meeting in 1914. In Williams' series of three or four cases the lesions were confined to the region of the finger nails and developed as onychiae. The infection remained localized in every case, but was so severe as to cause the loss of the nails in several instances. In at least one of the cases there have been mild recurrences every few months, but the lesions have always subsided on the application of tincture of iodin. Bacteriologic examination of the pus in these cases was made by Dr. Hans Zinsser, and all showed a typical blastomyces which grew in the usual way on culture mediums. With the exception of Williams' cases, those which occurred in Califor-

21. Morris, R. T.: A Case of Systemic Blastomycosis, Jour. Am. Med. Assn., 1913, lxi, 2043. Powers: Systemic Blastomycosis, Tr. Am. Surg. Assn., 1914, p. 89.

22. Hyde: Correspondence Respecting Blastomycosis, Jour. Cutan. Dis., 1907, xxv, 34.

23. MacGowan: Case Report of Blastomycosis, South. California Pract., 1906, xxi, 148.

24. Hill, H. P., and Dickson, E. C.: Report of a Case of Systemic Blastomycosis, California State Jour. Med., 1914, xii, 120.

nia differed in no respect from the cases which have been described elsewhere, and they prove conclusively that Hyde's explanation for the differences in the method of reproduction in *Oidium Coccidioides* and blastomyces is not correct.

Hektoen,[25] MacNeal and Taylor[8] and Brown and Cummins[13] have made experimental comparative studies of the two conditions, and they all agree with those who are familiar with the clinical cases of coccidioidal granuloma in believing that the two are distinct diseases, although they are closely related. The mere fact that both grow as similar fungi on artificial culture mediums is not sufficient ground for considering them identical. The constancy with which the characteristic methods of reproduction in the tissues is adhered to in each, irrespective of climatic influences, as well as the recognized differences in the clinical course of each would seem to be sufficient evidence that the two conditions are distinct. That they are closely related, however, there can be no doubt, and it seems quite probable that Ricketts[26] was correct when he said that "the differences between these diseases may all be explainable on the score of specific variations of the fungi concerned."

Diagnosis can be made only by the demonstration of the characteristic endosporulating bodies in the tissues, pus or sputum. The clinical picture is so varied, and the resemblance to tuberculosis and blastomycosis is so great, that one cannot depend on the clinical manifestations alone in making a diagnosis. The demonstration of the parasites is usually so easy that one has but to think of the disease and to make the necessary laboratory examinations to establish its identity. I believe that if a routine examination for the *Oidium coccidioides* were made in all cases of clinical tuberculosis in which the tubercle bacilli cannot be found, the number of recognized cases of coccidioidal granuloma would soon be greatly increased.

The prognosis is extremely grave. The outcome of the disease is almost always fatal. The duration varies from a few months to several years after the onset of the initial symptoms, but as a rule death follows in a few weeks or months after the infection becomes general. That recovery can take place is shown, however, by the two cases in which early operation was performed, and by an exceedingly interesting case (Case 38) which is included in the present series. The patient was a German laborer, aged 59, who entered the hospital complaining of severe gastro-intestinal disturbances. A diagnosis of car-

25. Hektoen, Ludwig: Systemic Blastomycosis and Coccidioidal Granuloma, Jour. Am. Med. Assn., 1907, xlix, 1071.

26. Ricketts: Oidiomycosis (Blastomycosis) of the Skin and Its Fungi, Jour. Med. Research, 1901, vi, 373.

cinoma of the stomach was established and gastro-enterostomy was done. He developed a postoperative pneumonia and died a few days later. At necropsy an old caseous focus which was surrounded by dense fibrous tissue was found in the base of the right lung. A diagnosis of "healed" tuberculosis of the lung was made, but on microscopic examination it was found that a number of typical spherical bodies of *Oidium coccidioides* were present, and that no tubercle bacilli could be demonstrated. There was no other evidence of any lesion which resembled tuberculosis.

Treatment is most unsatisfactory. The only hope seems to be in early amputation when the initial lesion is situated on one of the extremities and when there has been no further progression. In one of Gardner's cases, resection of the joint was sufficient to arrest the further progress of the disease; but it is probable that had the diagnosis been made before operation, more radical procedures would have been adopted. Roentgen-ray treatments have been tried in a few cases (Montgomery and Morrow[27] and Case 40), but, although there seemed to be some improvement in the local lesions, the onset of general infection was not prevented. Iodin, which is of value in blastomycosis, is of little aid in coccidioidal granuloma.[28] Autogenous vaccines have been tried, but they produced no beneficial effect. Neosalvarsan was tried by Cooke[12] without any signs of improvement. In fact, nothing that has been attempted in medication has had any appreciable effect in allaying the progress of the disease.[29]

CASE REPORTS

1. Coccidioidal Granuloma

Case 32.—Mr. D., a patient of Dr. Rixford's, was treated in Lane Hospital, San Francisco, during the spring and summer of 1907. The clinical record is unknown to me, but the following data are recorded in reports of the Pathological Laboratory. All the examinations were made by Dr. Ophüls.

April 20, 1907, a specimen from a resected knee was examined. Sections showed a marked formation of granulation tissue and extensive destruction of the cartilage. There were many tubercles in the synovial membrane, and many adult forms of the spherical bodies of *Oidium coccidioides*. Cultures showed the typical mold growth.

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27. Montgomery, D. W., and Morrow: Reasons for Considering Dermatitis Coccidioides an Independent Disease, Jour. Cutan. Dis., 1904, xxii, 368.

28. Cooke (Footnote 12). Brown and Cummins (Footnote 13). Hektoen (Footnote 25). Brown, P. K.: Coccidioidal Granuloma, Jour. Am. Med. Assn., 1907, xlviii, 743.

29. In addition to the references already given, the following will be found of interest: Montgomery, D. W., Ryfkogel and Morrow: Dermatitis Coccidioides, Jour. Cutan. Dis., 1903, xxi, 5. Montgomery, F. H., and Ormsby, O. S.: Systemic Blastomycosis: Its Etiologic, Pathologic and Clinical Features as Established by a Critical Survey and Summary of Twenty-Two Cases, Seven Previously Unpublished; the Relation of Blastomycosis to Coccidioidal Granuloma, The Archives Int. Med., 1908, ii, 1.

In May of the same year, scrapings of tissue from the wrist and from the knee showed much granulation tissue and much cicatricial tissue with many tubercles and large caseous areas. In the giant cells of the tubercles were many parasites in various stages of development. Pus from the wrist showed many endosporulating forms.

July 3, sections of recent lesions of the skin and scrapings from the wrist, knee and leg were examined. Sections from the skin showed marked cellular infiltration and formation of granulation tissue in the papillary layer of the cutis. There was marked irregular growth of the epithelium, which extended far into the granulation tissue, and there were several small abscesses containing parasites. The granulation tissue from the wrist showed many tubercles with extensive caseation and many giant cells.

CASE 33.—J. C., a French farm laborer, had lived near Colusa, Calif., for nearly twenty years. In the autumn of 1907 he went to the southern part of the state, "near Los Angeles," to assist in walnut picking. In January, 1908, he consulted Dr. C. A. Poage of Colusa on account of an abscess between the thumb and index finger of the hand. At the same time a small abscess developed on the side of the face, near the ear. Both lesions were opened and drained, but they refused to heal although numerous incisions were made. A few months later a similar lesion appeared on the dorsum of one foot. This was also incised, but did not heal. In May, 1908, the patient was referred to Dr. Stanley Stillman of San Francisco, who curetted the abscesses and sent the tissues to Dr. Ophüls for examination.

Sections showed vascular granulation tissue in which were many submiliary nodules consisting of epithelioid cells, with central caseation. Many mature forms of the *Oidium coccidioides* were found.

The patient complained of persistent cough and profuse expectoration, and on two occasions the spherical bodies of *Oidium coccidioides* were found in the sputum. Repeated examinations for tubercle bacilli proved negative.

The abscesses remained open and discharging, and the cough persisted until December, 1908, when the general health of the patient improved, the wounds healed and the cough disappeared. During the following year and until February, 1910, he remained in fairly good health and was considered cured, but at that time he began to show symptoms of subacute nephritis, and he died in November of the same year. During the terminal illness there was no evidence of recurrence of the skin lesions or of the pulmonary condition. Necropsy was not permitted.

CASE 34.—C. F. J., an Australian sailor aged 39, was admitted to the San Francisco Hospital, Feb. 14, 1909, on the service of Dr. J. B. Frankenheimer. The family history and the previous personal history were negative so far as the terminal illness was concerned. In October, 1909, the patient had obtained work as a rope-splicer in the oil fields of Kern County in the San Joaquin Valley. In December of the same year he began to cough, and in January, 1910, he became "short of breath" on exertion. Previously to that time he had had no fever, hemoptysis or night sweats.

On admission to the hospital he complained of pain in the left side of the chest, cough with free expectoration, frequent night sweats and a loss of 22 pounds in weight during the past three weeks. He had noticed some slight abrasions of the skin which had been obtained while he was working and which had become infected, but they had not been sufficiently severe to attract especial attention, and they had all cleared up before he came to the hospital.

The patient was moderately anemic, somewhat cyanotic and slightly dyspneic. There was a pleural effusion in the left side of the chest which reached the level of the fifth dorsal vertebra posteriorly, and which had displaced the heart so that the right margin of the area of cardiac dulness was well to the right of the right sternal margin. There was no evidence of cardiac valvular involvement, and the cardiac muscle tonus was not impaired. The liver and

the spleen were palpable. The skin was clear, the superficial lymph nodes were not enlarged, and the reflexes were normal.

Two thousand cubic centimeters of fluid were withdrawn from the pleural cavity, but it rapidly reaccumulated and was removed again within two weeks. The fluid on both occasions was clear and contained no demonstrable bacteria. Cultures were negative.

The Moro skin reaction was positive, but repeated examinations of the sputum revealed no tubercle bacilli. The urine was in no way abnormal. The red blood corpuscles numbered 4,800,000, and the leukocytes numbered 12,000. The differential count showed 87 per cent. polymorphonuclear neutrophils, 7 per cent. lymphocytes, 4 per cent. large mononuclear cells, 2 per cent. eosinophils and 1 per cent. basophils.

Early in June an enlarged gland was noticed under the sternocleidomastoid muscle, immediately above the sternoclavicular joint on the right side, and it rapidly increased in size and became very tender. At this time the patient was very weak, his appetite was poor and he had a very severe cough and many night sweats. Dulness was noted at the root of the right lung, and there were numerous moist râles in the right upper lobe. June 7, the gland was excised, and an abscess from which about 2 ounces of creamy pus escaped was revealed at the apex of the right pleural cavity. Sections of the gland were examined by Dr. Ophüls, who made the diagnosis of coccidioidal granuloma of the cervical lymph glands. The characteristic endosporulating forms were found in the tissue, and cultures showed a pure growth of the fungus. Subsequent examinations of the sputum showed numerous endosporulating forms of the *Oidium coccidioides*.

The patient gradually became weaker and there was progressing evidence of pulmonary involvement. A large tumor appeared under the left sternocleidomastoid muscle, and the cervical and inguinal lymph nodes became enlarged. The fever was intermittent and remittent in character, and was usually about 101 F. in the afternoon but occasionally reached 103. The respirations varied between 20 and 26, and the pulse between 90 and 116. The patient died, July 31, 1910.

Necropsy was performed by the author about twenty-four hours after death. Examination showed a general infection with the *Oidium coccidioides* involving the meninges, lungs, pleura, cervical, mediastinal and retroperitoneal lymph nodes, liver, spleen, kidneys, ribs and sternum. The macroscopic appearance of the lesions in the soft tissues was identical with that of tuberculosis, but in addition there were large abscess cavities in the neck and between the parietal layer of the pleura and the ribs which were filled with thick, creamy pus. Microscopic examination of the tissues revealed numerous spherical bodies with double-contoured capsules, many of which contained spore-like bodies. Cultures from the pus showed pure growths of the characteristic fungus. No tubercle bacilli were found in spite of prolonged search. The lesions were reproduced in guinea-pigs by inoculation of pus into the peritoneal cavity, and the fungus was again grown in pure culture from them.

CASE 35.—J. E. F., a brakeman on the Southern Pacific Railway lines in the San Joaquin Valley, was admitted to the Southern Pacific Hospital in San Francisco, July 8, 1911, complaining of a stiff and painful elbow. He stated that in 1902 he had received a blow on the elbow and that since that time he had constantly suffered pain. This had become progressively worse until one month before admission to the hospital, when it was so severe that he was forced to stop work.

On examination it was found that the right elbow was completely ankylosed and that there was marked atrophy of the muscles of the arm. There was no other evidence of disease. Local applications of heat and of high-frequency electricity were tried without benefit. August 8, resection of the elbow was performed by Dr. S. J. Gardner. Microscopic examination of the tissue was

made by Dr. H. W. Gibbons and Dr. Ophüls, who found that there was much granulation tissue with typical tubercle-like nodules, in some of which were the characteristic spherical bodies of *Oidium coccidioides*.

The patient made a slow recovery, but finally returned to work and has regained a fairly good use of the arm. He was still in good health a few months ago, and has shown no evidence of recurrence.

Case 36.—N. S., a Hindu laborer aged 26, admitted to the surgical ward of Lane Hospital, May 25, 1912. But little was learned of his previous history excepting that he had recently been in a hospital in Stockton on account of a condition of the knee which was thought to be tuberculosis. On admission to Lane Hospital, the patient was much emaciated and there was an open wound in the left knee from which much foul-smelling pus escaped. May 29, the knee was resected, but the wound continued to discharge much pus and the patient failed to improve. He complained of great pain in the knee and subsequently of pain in the left elbow, which became swollen and stiff. He remained in the hospital until August 27, when he died.

Necropsy was performed by Dr. Ophüls about twenty-four hours after death. Examination revealed a general infection with the *Oidium coccidioides*, involving the lungs, pleura, cervical, mediastinal and peribronchial lymph nodes, synovial membranes of the left elbow and the lumbar vertebrae. There was marked caseous destruction of the bodies of the vertebrae, and an abscess cavity extended along the course of the left iliopsoas muscle into the pelvis. Smears of the pus and of scrapings from the peribronchial lymph nodes and from the synovial membrane showed many characteristic endosporulating forms of the *Oidium coccidioides*. No tubercle bacilli were found. Sections of the tissues showed the typical tubercle-like nodules and many of the spherical bodies.

Case 37.—A Mexican laborer who could speak no English was seen by Dr. T. M. McNamara of Bakersfield in the autumn of 1912. The patient was practically moribund when first seen, and no history could be obtained. Necropsy was performed by Dr. McNamara, who found a condition which resembled disseminated miliary tuberculosis. Portions of the lung and of the spleen were sent to the author for microscopic examination. Sections showed numerous lesions which resembled tubercles, but which contained many double-contoured bodies of the *Oidium coccidioides*. No tubercle bacilli were found.

Case 38.—J. U., a German laborer aged 59, was admitted to the medical ward of Lane Hospital, July 19, 1913. He complained of "pain in the bowels," which came on about four hours after eating and which was relieved by pressure. He had lived in Germany, the Sandwich Islands and California, but there is no record of what parts of California he had visited. Diagnosis of duodenal obstruction was made, and laparotomy was performed, August 5. At operation an inoperable carcinoma of the stomach was found, and gastro-jejunostomy was done. August 15, the patient contracted pneumonia, and he died a few days later.

Necropsy was performed by Dr. E. D. Downing about twenty-four hours after death. Examination revealed a large polypoid carcinoma situated on the lesser curvature of the stomach near the pylorus. There was a well-marked pneumonia of the left lower lobe, and an area of gangrene in the right upper lobe. In the base of the right lung was an old caseous focus which was surrounded by dense fibrous tissue and which was thought to be a "healed" tuberculous process. However, microscopic examination made by Dr. Ophüls was recorded as follows: "A section of the lung shows large, old, caseous areas surrounded by dense fibrous tissue. At the edge of the caseous material there are a number of double-contoured capsules of the *Oidium coccidioides*. The majority of them are empty, but some contain a little granular protoplasm. Diagnosis: healed coccidioidal granuloma of the lung." No other foci of coccidioidal granuloma were found.

CASE 39.—In August, 1913, Mrs. H., an American housewife aged 65, consulted Dr. John E. Veon of Bakersfield, Calif., complaining of pain in the left ankle which had persisted for eight weeks. A localized tender swelling was found immediately above the outer malleolus, and there was daily intermittent fever which ran from 100 to 103 F. In November, 1913, the tumor was incised and a small abscess was drained. The wound refused to close. In February, 1914, the bone was curetted, and the material was sent to Dr. Ophüls for examination. Sections showed the characteristic lesions of coccidioidal granuloma, in which were many of the usual spherical endosporulating bodies.

About this time the patient complained of pain in the right knee, but this soon disappeared and remained absent for about six months. The abscess cavity in the left ankle gradually healed after prolonged treatment with liquor formaldehydi, tincture of iodin and Beck's paste. During the summer of 1914 the patient was free from symptoms, but about September 1 she began to complain of a recurrence of pain in the right knee. At the last report, a few months ago, the knee was swollen, hot and painful, and there were four small painful nodules on the shaft of the right tibia, but the patient appeared to be normal in all other respects.

CASE 40.—J. D., a Jamaican negro sailor aged 21, came to the Outpatient Department of the Leland Stanford Junior University, School of Medicine, Jan. 31, 1914, complaining of a sore foot. He appeared to be in great pain and was unable to put the right foot to the ground. There was an area of discoloration on the dorsum of the foot in the region of the middle cuneiform bone. The whole foot was swollen and somewhat tender, the greatest tenderness being located immediately beneath the discolored area. A diagnosis of arthritis of doubtful origin was made, and the patient was sent to the San Francisco Hospital where he was admitted to the Surgical Service of the Leland Stanford Junior University, School of Medicine. At the time of admission, a tentative diagnosis of tuberculosis was made.

The patient dated his illness from a time two years previously when he had been suspended by the feet for several hours in Honduras. He came to California in July, 1913, and soon after his arrival he went to Coalinga where he worked in the oil fields for four months. During that time he had no cough and he felt practically well. In November, 1913, he returned to San Francisco, and, a few days later, following exposure from sleeping outdoors, he began to cough. There was no fever and no blood in the sputum at that time.

November 11, a heavy iron girder fell on his right foot, and he was forced to stop work. The foot became swollen, and pained considerably. He treated at home for about two weeks by applying liniments, but although the pain disappeared, the swelling persisted. He then consulted a physician, who had a Roentgen-ray examination made and who placed the foot in a plaster cast. The pain continued to be so severe that the patient insisted on removing the cast, and he was therefore discharged from the hospital in which he was being treated.

A few days after his admission to the San Francisco Hospital, the skin over the tender area broke and there was a profuse discharge of bloody pus. The foot was again placed in a plaster cast, but the discharge did not cease. March 3, the patient was removed to Lane Hospital, where Roentgen-ray examination was made and a diagnosis of tuberculosis of the tarsal bones was given. Several Roentgen treatments were given at this time, and another series was given during the interval between April 3 and 20; but although the treatments relieved the pain to a certain extent, the suppuration continued and new sinuses formed. During the time that he was in Lane Hospital, the temperature was septic in type, varying from 98 to 99 F. in the mornings and from 102 to 103 in the afternoons. The same type of temperature persisted after he returned to the San Francisco Hospital, and he steadily lost weight and strength.

May 2, Dr. Rixford amputated the foot and curetted the pockets, which had extended along the course of the tendons. The general condition improved

after the operation, and the patient began to gain in weight. During June and July, fluctuating masses appeared on the right side of the chest, on the side of the left leg and in the right arm. These were still present when the patient left the hospital in September, although he felt and looked quite well. After leaving the hospital, the patient left San Francisco for New York, and it is supposed that he is now in Jamaica.

Bacteriologic examinations of the pus were made by me with the assistance of Dr. E. G. Cary. March 19, 1914, a specimen of pus from the foot was examined. The smear showed a moderate number of pus cells and of lymphocytes and a few large mononuclear cells. There was a moderate amount of fibrin. No tubercle bacilli or other bacteria were found, and no spherical bodies of the coccidioidal type were seen. The culture on agar agar was reported negative after forty-eight hours, but some time later a growth of mold was found in the tube. A portion of the pus was injected into the peritoneal cavity of a guinea-pig, but no lesions were found when the animal was killed a month later.

June 3, another specimen of pus was obtained, and in this a few atypical spherical bodies with double-contoured capsules were found. No bodies containing endospores were seen. Culture of this specimen showed the characteristic mold growth in a few days, and in a hang-drop culture the development of the mycelial threads from the spherical bodies was observed. Two guinea-pigs and one rabbit were inoculated with the pus and in all, after one month, the characteristic lesions of coccidioidal granuloma were found. Pus from the lesions in all the animals contained the typical endosporulating bodies, and cultures showed pure growths of the fungus. No tubercle bacilli or other bacteria were found in the original pus or in that obtained from the lesions in the animals.

2. Systemic Blastomycosis

Case 1 (Previously reported by Hill and Dickson[4]).—A. S., a Greek laborer aged 28, was admitted to the San Francisco Hospital on the Stanford University Medical Service, July 6, 1912. He had been working at McCloud, Calif., during the summer months and in the Sacramento Valley during the winters. Six months before admission, while working at McCloud, he "caught cold and began to spit blood." The "cold" lasted for two months. One month later he noticed a swelling under the left lower eyelid, and this was followed by similar swellings on the forehead, face, arms and legs. At intervals the swellings on the face would open, discharge a quantity of pus and dry up. The patient gradually lost weight and strength, although there was no loss of appetite.

At the time of admission, the patient was emaciated, pigmented and covered with nodular masses, discharging ulcers and dried crusts. There was a slight cough and much mucopurulent sputum, which was occasionally streaked with blood. The cervical lymph nodes were shotty. Fluctuating masses were situated under the skin in various parts of the body, and there were numerous discharging ulcers and scars of old ulcers. The skin over the fluctuating masses was normal in color excepting at the point of rupture, and these areas were rarely painful or tender, excepting around the joints. The abscesses showed a marked tendency to involve the deeper tissues and the bone. There was evidence of extensive involvement of both lungs.

Examination of the aspirated pus was made by Dr. Ophüls, who found typical budding forms of blastomyces, and subsequently similar forms were found in large numbers in the sputum. Repeated examinations for the tubercle bacillus were negative.

The course was that of a chronic pyemia with septic temperature, progressive emaciation and loss of strength. There were numerous recurring abscesses involving the subcutaneous tissues, deeper tissues, bones and testicles. Death occurred about six months after admission to the hospital.

Necropsy was performed by the author about twenty-four hours after death. Examination showed a general infection with blastomyces involving the skin, subcutaneous tissues, bones, cartilages, lungs, kidneys and testicles. A peculiar type of bone involvement was noted in the ribs, where superficial subcutaneous abscesses were found to be continuous with intrathoracic abscesses through perforations in the ribs, while the soft intercostal tissues remained intact.

Smears from the pus from the various abscesses showed numerous budding forms of the blastomyces, and cultures showed fungus growth. Sections of the tissues showed many small tubercle-like nodules in which were the characteristic spherical and budding forms. No tubercle bacilli were found in the pus or in the lesions in the tissues.

Several guinea-pigs and rabbits were injected with the pus, but in none were any lesions found. Inoculation of animals with the fungus also proved negative.

CASE 2.—D. McC. consulted Dr. J. L. Mudd of Merced, Calif., in the summer of 1911 because of a pustular eruption on the thumb and dorsum of the left hand. He was a native of Michigan and had recently moved to California because of "lung trouble." The family history was unimportant excepting that one brother had died of tuberculosis and that the patient had cared for him during the last three months of his illness. His general health had been good until May, 1910, and he had worked in a grain elevator where there was a great deal of dust. His illness began with a cough and with sharp pain in the right side of the chest. The cough became progressively worse, there was much thick, blood-stained sputum, and finally there was spontaneous hemoptysis without coughing. The patient said that tubercle bacilli had never been found in the sputum.

He was "sick all summer;" had anorexia, nausea and vomiting, high fever in the afternoons, frequent night sweats, dyspnea, progressive weakness, rapid pulse rate and rapid loss of weight. After coming to California he improved in general health, the cough disappeared and he was able to work as a farm laborer.

In March, 1911, he noticed a "pimple" on the back of the thumb which became pustular and discharged a small amount of pus. A small ulcer formed which progressively enlarged in all directions. In May a similar nodule appeared on the same thumb, and it also resulted in the formation of a progressively enlarging ulcer. There were burning and itching in both lesions, but there was never any pain. In October, 1911, the lesions were examined by Dr. Ophüls, who gave the following report: "Large superficial ulcer on extensor surface of thumb and another on the adjoining part of the hand. Ulcer on thumb covers practically the entire extensor surface; the other is round, about 3.5 cm. in diameter. The floor of the ulcers is rough, somewhat papillary, and covered with crust. The edges are elevated. At the edges and on the floor of the ulcers are miliary abscesses which discharge pus on pressure. In the pus are many flat, horny epithelial cells and a moderate number of spherical fungi with double-contoured capsules, some of which show budding."

The patient continued in fair health and was able to work until the latter part of January, 1912, when he was kicked in the back by a horse. A short time later he noticed a pain in the left lumbar region which became more severe until there was sharp, throbbing pain which extended into the left groin, the region of the bladder and the left testicle. The pain was paroxysmal and occurred mostly at night. There was frequent urination. Examination showed tenderness in the region of the left kidney and a few red blood corpuscles in the urine. The pain and disability became worse until the patient was forced to remain in bed, and frequent hypodermic injections of morphin were necessary. Soon a septic type of temperature and evidences of an abscess in the region of the left kidney developed. Operation was performed and a large perirenal abscess was drained, but the patient did not recover sufficiently to

leave his bed. He became very much emaciated, developed a severe cough, had much sputum and numerous night sweats. The temperature remained septic in type. The sinus from the perirenal abscess continued to discharge, and the patient constantly suffered from very severe pain. He died, June 13, 1912.

At necropsy, the second and third lumbar vertebrae were found to be almost completely destroyed, and they were replaced by a large abscess cavity. There were a few small cavities in the lungs and a few small abscesses in the subcutaneous tissues of the arms. There was no complete record of the necropsy findings, and no bacteriologic or histologic examination was made of the materials obtained.

In closing, I wish to express my thanks to Professor Ophüls for permission to use the records of the Division of Pathology, and to the various gentlemen mentioned in the protocols for their courtesy in sending me the clinical records of their cases.

CONCLUSIONS

1. Cases of coccidioidal granuloma have occurred with sufficient frequency to establish the disease as a clinical entity.

2. The condition so closely resembles tuberculosis as to be practically indistinguishable unless the characteristic parasite is recognized.

3. It is probable that many cases are diagnosed tuberculosis, and that if routine examination for the parasite were made in cases which are clinically tuberculosis but in which the tubercle bacillus cannot be found, the number of recognized cases of coccidioidal granuloma would rapidly increase.

4. Coccidioidal granuloma and blastomycosis, though closely related, are etiologically distinct.

5. Although the great majority of cases of coccidioidal granuloma prove fatal, the progress of the disease may be prevented in a few cases by radical removal of the infected parts.

6. A very small proportion of the cases may undergo spontaneous recovery.

A CASE OF ACUTE MILIARY TUBERCULOSIS

SHOWING THE BLOOD PICTURE OF AN ACUTE MYELOGENOUS LEUKEMIA *

MARK MARSHALL, A.B., M.D.
ANN ARBOR, MICH.

The case I report came under my observation Nov. 21, 1914, one month after the beginning of the illness. The following history was obtained from the attending physician, Dr. William Blair:

Mrs. B., a housewife, aged 52, had an unimportant family history except that her mother died of cancer. There was no history of tuberculosis in either branch of the family. With the exception of a rather severe rheumatic fever nineteen years ago, the patient has been unusually strong until the beginning of the present trouble. This began one month ago with a feeling of unusual fatigue and slight fever. The elevation of temperature has continued to the present time and has been irregularly remittent ranging from normal to 103.8. There have been chilly sensations at times but never a definite rigor. On Oct. 27, 1914, two days after the beginning of the illness, the blood count was as follows: erythrocytes, 3,000,000; leukocytes, 16,480; hemoglobin, 85 per cent. (Sahli).

Physical Examination.—Oct. 21, 1915: This showed a medium-sized woman, stuporous for the most part but showing irritability when disturbed. Temperature 101.8, pulse 116, respiration 26. There was a marked pallor of the mucous membranes. The skin was manifestly anemic but showed a slight cyanosis, as well as a decided icteroid tint similar to that which characterizes pernicious anemia. Panniculus adiposus was abundant, strikingly so in view of the apparent severe anemia and marked toxemia. There were no glandular enlargements. The eyes followed the moving finger poorly owing to difficulty in maintaining attention. The pupils were equal and reacted both to light and accommodation. There was no rigidity of the neck muscles. Knee-jerks were exaggerated, Babinski and Kernig negative. There was a marked ankle clonus. The heart and lungs were negative. The liver was distinctly palpable almost a hand's breadth below the costal margin but was not tender. The spleen was palpable. The abdomen was tympanitic throughout, not distended and not tender. The blood findings on the above date were the following: erythrocytes, 1,320,000; leukocytes, 23,840; hemoglobin, 20 per cent. (Sahli).

On account of the prolonged irregular temperature with a leukocytosis, a rapidly progressing anemia and the absence of signs of any localized disease, a provisional diagnosis of streptococcus septicemia was made. A blood culture made on the above date with alkaline bouillon gave negative results, however.

November 23: The maximum temperature was 101.4. There was increased weakness and cyanosis, and breathing was somewhat labored. The urine showed trace of albumin and a large number of casts. Hemoglobin, 15 per cent. (Sahli); leukocytes, 13,000.

November 24: The urine contained a trace of albumin and a very few casts, but was negative for Bence-Jones bodies.

November 26: Maximum temperature 100.4 F. There was definite loss of strength and more marked stupor.

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November 28: The patient complained of air hunger which steadily increased during the day. Was somewhat relieved by lowering the head, bandaging the legs and administering oxygen.

November 29: Air hunger greatly increased. Pulse 150. Respiration 50. Patient died, apparently an anemic death, the air hunger being the most striking feature for the last twenty-four hours of life.

A differential count made two days before the patient's death gave the following results: Polynuclear leukocytes, 42.5 per cent.; lymphocytes, 4 per cent.; large mononuclears, 18.5 per cent.; myeloblasts, 2.4 per cent.; premyelocytes, 1.8 per cent.; myelocytes, 30.4 per cent.; the total myelocytic forms being 34.8 per cent.; 2 nucleated reds were found in the one preparation.

The necropsy report by Dr. A. S. Warthin was as follows:

Nov. 29, 1914: Pathological Diagnosis: Primary tuberculosis of bronchial nodes. Healed tubercle in right lung. Miliary tuberculous focal necroses in lung, liver, spleen and bone marrow. Cold abscesses in bronchial nodes; secondary pyogenic infection; rupture of abscess into pulmonary vein. Older miliary tubercles in kidney. Tubercle bacilli colonies in myocardium. Exhaustion of bone marrow. Secondary anemia gravis aplastica, so-called. Chronic fibroid salpingitis. Fatty degeneration of heart and liver. Multiple thromboses in pulmonary veins, portal vein and ovarian plexus.

General External Examination: Build: slender; body length 162 cm. Body bloodless, small amount of blood in veins. Mammae atrophic. No nodules in breast. Cervical and axillary nodes not palpable, inguinal just palpable. Splenic dulness does not extend below edge of ribs.

Eyes: Conjunctiva of slight lemon color.

Thorax: Somewhat depressed. Epigastric angle less than right angle. Moderate corset thorax.

Abdomen: Below level of ribs. Negative on palpation.

Skin: Pale, translucent; brunette, more pigmentation over face and flexor surfaces. Pigmented moles over face, shoulders and neck, some paler with no pigment.

Teeth: Those remaining are in bad condition; a number are false.

Mucous Membranes: Pale, bloodless. Gums pale — no lead line.

Rigor Mortis: In chin and hands. Absent in feet and legs.

Panniculus: Abundant.

Edema: Moderate in lower extremities, trace throughout body.

Hypostasis: Pale.

Ears: Negative.

Genitalia: Negative.

Thorax and Abdomen (main incision): Panniculus: Pale yellow, with coarse lobules, almost bloodless, moist, shining.

Musculature: Bright, shiny, red, as in carbon monoxid poisoning.

Omentum: Shows small amount of fat.

Position of Abdominal Organs: Spleen extends to edge of ribs. Liver is hand's breadth below ensiform, finger's breadth below ribs.

Mammae: Right atrophic, shows small amount of tissue, mostly fat. Left shows more gland tissue.

Costal Cartilages: Cut easily, except first on left, which is calcified. Sternum: moderately osteoporotic, shows no thickening of periosteum.

Thorax: No fluid in left pleural cavity, about 300 c.c. of clear fluid in right. Lungs free; distinct, firm nodules back of suprasternal notch. Apex of heart behind fifth rib in left parasternal line.

Anterior Mediastinum: Mediastinal fat lemon yellow.

Thymus: Thymic fat is firm and replaced by definite firm nodules. On section shows hyperplastic lymph nodes — firmer and more translucent than normal.

Pericardium: Pericardial tension not increased. Fluid increased and blood-tinged. Small patches of recent pericarditis.

Heart: Flabby, smaller than cadaver's fist. Large soldier spot over anterior wall of right ventricle. Small amount of blood in great vessels. Auricles collapsed, contain pale clots and small amount of blood. Fatty degeneration of muscle of right ventricle. Right ventricle measures 7 mm., 4 mm. of which is fat. Left ventricle measures 12 mm.; fatty degeneration of muscle. Mitral valve admits three fingers; flaps negative. Tricuspid valve admits three fingers.

Left Lung: Airless, filled with pin-point and larger nodules, a conglomerate nodule, size of cherry. On section, lung shows edema, congestion and numerous miliary nodules, not caseating, translucent, firm, rising above surface, and more red than tubercles.

Right Lung: Heavy. Pleura shows numerous white, firm nodules — most marked on posterior surface. Largest nodule is size of a cherry, umbilicated, in upper lobe. On section it is seen to be an encapsulated, caseated tubercle. Lung on section shows marked edema and everywhere miliary tubercles of all sizes, none showing caseation.

Neck: Trachea: Bronchial glands enormously enlarged — size of small orange — surround trachea, which on section show multiple abscess cavities containing greenish pus. Abscess wall is smooth, covered with creamy gray material — no sulphur granules visible. In a gland whose structure is preserved there are no distinct tubercles. Thyroid: slightly enlarged; abundant colloid.

Abdomen: Peritoneum: Moist, shining throughout.

Spleen: Not adherent, large, firm. Shows small miliary nodules through capsule. On section is seen to be completely strewn with miliary nodules, raised. Two of the larger nodules on scraping show central softening.

Large Intestine: Transverse colon shows W fold descending to pelvis. Descending colon and cecum filled with soft gray feces and gas. No neoplasm in any part of intestinal tract.

Appendix: Adherent to ovary, broad ligament and bladder; buried in fat; 3 cm. long; lumen partially obliterated — old chronic obliterative appendicitis.

Duodenum: Shows slight brownish mucus.

Stomach: Empty. Fundus contains about a pint of fluid and gas. Mucosa of stomach very pale, smooth. Mucosa of fundus atrophic. No neoplasm.

Pancreas: Shows normal firmness, pale. Lobules normal. Nothing pathologic.

Liver: Moderately large, edges fairly sharp. Capsule thick near ligaments. Over entire surface are numerous miliary nodules of all sizes. Upper pole shows hemangiocavernosum 30 by 20 mm. On section liver is pale, chocolate-brown; lobules slightly smaller than normal. Cloudy, opaque, innumerable nodules from pin-point to mustard seed in size, without caseation.

Gallbladder: Empty, opaque, long, pendulous, thick.

Left Adrenal: Normal in size. In medulla are nodules pin-head in size, firm, hyaline, without caseation.

Kidneys: Left: Fatty capsule abundant. Fibrous capsule strips easily. Surface smooth. Shows slight traces of fetal lobulations. Same kind of nodules as seen elsewhere. Cut surface is pale, cortex atrophic, parenchyma cloudy. Pelvis negative. Ureter negative. Right kidney: resembles left in every way. Retroperitoneal lymphnodes are hyperplastic.

Pelvis: No neoplasm in pelvis. Rectum negative.

Bladder: Distended. On section, mucosa otherwise negative.

Uterus: Hard, fibrous, but no neoplasm. Uterus small. Endometrium very atrophic. Cervix shows old lacerations, catarrh. Right tube and fimbriated appendage adherent to appendix and cecum. Cecum and tube are stretched. Ovaries show fibroid atrophy, more marked in right.

Special Regional Examination: Ribs and vertebrae are negative; the marrow is very dry, exhausted.

Microscopic Findings: Lungs: Miliary areas of coagulation necrosis containing colonies of tubercle bacilli. A few show beginning tubercle formation. Marked edema. Nodule in right lung is an old hyaline, calcified, healed tubercle. No active tubercles about it.

Bronchial Nodes: Multiple cold abscesses. Tubercles with secondary infection. Large caseous tubercles.

Heart: Old scleroses of epicardium. Fatty infiltration of epicardium with serous atrophy. Marked fatty infiltration of heart muscle. Fatty degeneration of muscle with atrophy. Small areas of leukocyte infiltration in the myocardium — localization of tubercle bacilli. Sclerotic patches in endocardium. Marked fatty degeneration and Zenker's necrosis of papillary muscle. Clots from heart are white, containing few red blood cells but enormous numbers of atypical nucleated cells resembling myeloblasts, atypical myelocytes and bone-marrow lymphocytes.

Liver: Multiple focal necroses, coagulation and caseation. Numerous localized collections of lymphocytes. Tuberculous thrombus in portal vein branches. Some few lesions show beginning tubercle formation, but the majority are the primitive lesions produced by tubercle bacilli. When stained for tubercle bacilli these areas show pure colonies of bacilli. Acute passive congestion and fatty degeneration.

Spleen: Acute passive congestion. Multiple foci of coagulation and caseation necrosis containing pure colonies of tubercle bacilli. No fully developed tubercles.

Kidneys: Cloudy swelling. Acute passive congestion. Atrophy. Dilatation of tubules. Numerous hyaline glomeruli. Few miliary tubercles, older and larger than lesions in lung, liver and spleen. Adrenals, fatty degeneration. Atrophy. No tubercles.

Cervix: Cervical catarrh and cystic glands; endometrium, atrophic. Fallopian tubes, chronic fibroid; healed salpingitis. Ovary, hyaline laminated thrombus in ovarian plexus.

Bone Marrow: Exhaustion of red-cell forming marrow. Small points of coagulation and caseous necrosis in the marrow. Numerous atypical myelocytes and myeloblasts.

Before discussing this very unusual leukocyte picture, it would be well to consider the blood findings which usually obtain in acute miliary tuberculosis, as well as in other forms of tuberculous infection. Until within the last few years very little attention was paid to the differential leukocyte count as a possible means of differential diagnosis in those infections, characterized by normal or diminished total leukocyte counts, of which typhoid fever and acute miliary tuberculosis are the most frequently encountered examples.

Steffen,[1] in his researches on the blood findings in pulmonary tuberculosis, demonstrated that at least in cases making favorable progress there is a marked relative lymphocytosis, and any increase that may occur in the polynuclear elements he ascribed to the beginning of a secondary infection. It has been quite generally accepted that the tubercle bacillus, occurring alone, calls into action only the lymphoid elements of the blood inasmuch as tubercle formation requires

1. Steffen: Ueber Blutbefunde bei Lungentuberkulose, Deutsch. Arch. f. klin. Med., 1910, xciii, 355.

only these elements, in addition to the epithelial and giant cells, for its consummation, the leukocytes playing no part whatever in this process. Mathes,[2] however, has shown that in uncomplicated miliary tuberculosis, a condition in which the possibility of secondary infection can be more easily ruled out than in pulmonary tuberculosis, it is the rule to find a relative increase of the polynuclears with a corresponding decrease in the lymphocytes, the total count varying from normal to a rather marked leukopenia. This work of Mathes has been recently verified by Wack[3] of the Marburg clinic who reports seven cases of acute miliary tuberculosis with differential blood counts. He makes the very interesting observation that at the beginning of the illness there may be little if any reduction in the number of lymphocytes but, as the disease progresses, there is a gradual diminution in the number to as low as 3 or 4 per cent. with a total count of 5,000 and 6,000. Nägele[4] has shown that in typhoid fever, on the other hand, particularly in its late stages with severe leukopenia, the lymphocytes are relatively increased and may comprise one-half of the white blood cells.

In meningeal tuberculosis where one usually finds a slight or moderate leukocytosis, Wack finds that here, also, the increase affects only the polynuclears, the lymphocytes remaining unchanged or decreased in number according to the stage and severity of the disease just as was found in uncomplicated miliary tuberculosis. On the contrary, in all other forms of meningitis while there may be only a moderate leukocytosis, the lymphocytes as well as the polynuclears are increased in number.[5]

Turning now to my own case, we find, first of all, instead of a leukopenia, a rather marked leukocytosis, the minimum count being 13,000, the maximum 23,000. *A priori,* this would suggest either a secondary infection or perhaps an accompanying tuberculosis meningitis. The latter, while not ruled out by a postmortem examination of the central nervous system, can, I think, be excluded as a cause for the leukocytosis, for the increased white count was noted very early in the course of the infection, three days after the beginning of the illness. Had this marked the beginning of a meningitis surely some clinical evidence of meningeal irritation would have developed within a period of five weeks. If one should regard the suppurating bronchial nodes as the cause for the increased leukocyte count, one

2. Mathes: Die Diagnose der Miliartuberkulose, Med. klin., Breslau, 1912.

3. Wack, P.: Ueber Leukocytenbefunde bei Miliartuberkulose und ihre diagnostische Bedeutung, Deutsch. Arch. f. klin. Med., 1914, cxv, 596.

4. Nägele: Blutkrankheiten und Blutdiagnostik.

5. Rusca: Das Blutbild der Meningitis Cerebrospinalis epidemica und dessen diagnostische und prognostische Bedeutung, Deutsch. Arch. f. klin. Med., 1911, ciii, 235.

would still be left without sufficient pathology to account for the striking changes in the differential count. On the other hand, the miliary tuberculosis in this case showed an unusually extensive dissemination, a remarkable number of bacterial foci showing only the coagulation necrosis of recent bacillus localization. The unusual virulence of the tuberculosis furnishes the only satisfactory explanation for the appearance of immature leukocyte forms in the blood stream. There was certainly no general septic process, for the blood was found to be sterile seven days before death and there were no metastatic septic foci found at necropsy.

We are dealing, therefore, with a comparatively simple clinical factor inasmuch as there existed no such complication as might be expected to produce striking modifications in the leukocyte production. In view of the postmortem findings, therefore, this blood picture was a very unusual one. In addition to there being a large number of immature forms of leukocytes, there were striking deviations from the accepted morphologic standards of the various types of leukocytes. This was true to such an extent that many of the cells were difficult to classify. All forms were very poorly granulated. Many of the polynuclears were entirely without granules, as were also many of the myelocytes. Granulation, therefore, could not be used as a means of identification. This lack of granules often resulted in a striking similarity between certain of the more mature myelocytic forms and the large mononuclears. The relative size of the nucleus, its structure and staining properties was, therefore, made the basis of differentiation, particular attention being paid to the maturity of the nucleus. While the classification adopted might be looked upon as rather arbitrary, it is nevertheless one that purposely avoids controversial questions. All nongranular cells with a homogeneous basophilic cytoplasm and a round or oval deeply staining structureless nucleus, were classed as lymphocytes regardless of size. All cells with relatively large faintly staining oval or indented vesicular nuclei, were classed with the myelocytic forms. All mononuclear forms larger than a normal polynuclear, showing relatively small well-matured nuclei, were designated as large mononuclears regardless of the shape of the nuclei; and I may say that practically all the cells placed in this group correspond to the *Macroleukoblasten* (*pathologische Monocyten*) of Pappenheim.[6] With no desire to favor any one of the various theories of leukocyte development or to advocate any one system of nomenclature, the writer

6. Pappenheim, A.: Atlas der Menschlichen Blutzellen, 1905. Unsere derzeitigen Kenntnisse und Vorstellungen von der Morphologie, Genese, Histiogenese, Funktion und diagnostischen Bedeutung der Leukocyten, Ergebn. d. inn. Med. und Kinderh., 1912, viii, 183.

has, however, as a matter of convenience and uniformity, adhered to Pappenheim's classification and terminology.

Some unusual myelocytic forms were observed, that is, there were some showing deeply lobulated nuclei and others with larger horseshoe shaped nuclei resembling that of the so-called transitional cell except the nuclear structure was very immature, being faintly stained, more or less homogeneous and vesicular in appearance. The polynuclears were very poorly developed, being almost entirely nongranulated, and rarely were the nuclei divided. There were no eosinophils. The red cells showed very little change, considering the severity of the anemia. Only two nucleated forms were found in any one preparation. The cells reacted to the stain uniformly and there was practically no poikilocytosis or anisocytosis.

This case is a particularly interesting one when viewed purely from the clinical standpoint, for inasmuch as it presented no positive diagnostic points either in the history or in the physical examination, the striking blood picture immediately became a point of unusual interest and was naturally looked on as holding the key to a positive diagnosis. Obviously the question of a possible acute leukemia was the first to command attention. With the unusual number of immature forms and with numerous atypical forms of the various ages of leukocytes, acute leukemia could not be ruled out. The short course of the disease together with the severe anemia would also favor the diagnosis of acute leukemia or more nearly, perhaps, that poorly defined clinical entity leukanemia. In fact, some of the reported cases of acute leukemia have shown a percentage of myelocytic forms no higher than the case under discussion. Neither does the absence of a very high leukocyte count speak against such a conception, for a number of cases of acute leukemia have been reported in which there was no increase in the leukocytes.

Quincke,[6] Nana, Dock[7] and Warthin have reported cases of chronic myelogenous leukemia, complicated by acute miliary tuberculosis in which, during the course of the terminal tuberculosis, the leukocyte count dropped to normal and some of the reported cases showed at necropsy complete disappearance of the myeloid changes. The case under discussion would scarcely fall into this class for there had been no such previous ill health as would suggest a chronic leukemia. In this case, therefore, the absence at necropsy of all leukemic changes and the finding of an uncomplicated miliary tuberculosis leaves us with

7. Quincke: Leukämie und Miliartuberkulose, Deutsch. Arch. f. klin. Med., 1902, lxxiv, 445.
8. Dock: Am. Jour. Med. Sc., 1904, cxxvii, 563.

only the tuberculosis to account for the peculiar leukocyte picture. The latter, since it is not in accordance with the usual leukocyte finding in miliary tuberculosis as shown by the researches of Mathes and Wack, would, I believe, have to be looked on as due to a peculiar susceptibility of the individual. One need not regard the peculiar reaction of the myeloid tissue in this instance, in the light of a specific response to some peculiarity in the infecting organism, for this tendency for immature forms to appear in the circulating blood has been frequently observed in infections with such other organisms as the pneumococcus and streptococcus, and has been regarded as a manifestation of very poor resistance on the part of the infected individual. Why should not the same thing occur in infections with the tubercle bacillus, an organism which possesses in common with the pneumococcus and streptococcus the power of calling forth neutrophil polynuclears in relatively if not in actually increased numbers? That such a leukocyte picture should be found very rarely in infections with the tubercle bacillus as compared with infections with the streptococcus and allied organisms, is only in accordance with the hypothesis and should not constitute a reason for seeking some other explanation of the phenomenon. To be sure one would have to consider the possibility of an extension of the tuberculous process into the bone marrow, leading to destruction of a portion of the marrow and an abnormal activity of the remaining portion. This condition, however, was not found at necropsy.

On searching the literature for similar cases, one finds a report by Otto Roth[9] of a case of subacute miliary tuberculosis with the blood finding of a myeloblastic leukemia. A woman 50 years of age died of a subacute illness characterized by fever, swelling of the lymph glands, a severe anemia and a hemorrhagic tendency. The differential leukocyte count was as follows: Neutrophil polynuclears, 3.6 per cent.; premyelocytes, 2.2 per cent.; neutrophil myelocytes, 1.3 per cent.; myeloblasts, 76.6 per cent.; eosinophils, 0.1 per cent., lymphocytes, 15.6 per cent. Large mononuclears and transitionals, 0.6 per cent.

Necropsy showed a subacute miliary tuberculosis with recent septic foci in the spleen and parotids (staphylococcus infection). I am indebted to Roth for the review of the literature of the subject prior to 1913. Kast[10] reports a case in a child 15 months old with advanced tuberculosis of the bronchial glands and upper lobe of the left lung, as well as miliary tuberculosis of the liver, spleen and kidneys (bone

9. Roth, Otto: Ueber einen bemerkenswerten Blutbefund bei einem Fall von sub-akuter Miliartuberkulose, Ztschr. f. klin. Med., 1913, lxxviii, 75.

10. Kast: Med. Klin., Breslau, xviii. Referred to in München. med. Wchnschr., 1902, xlix, 2093.

marrow normal). The case presented a peculiar form of leukocytosis which led to the diagnosis of leukemia. Myelocytes, 31 per cent.; polynuclear leukocytes, 32 per cent.; eosinophil cells, 7.5 per cent.; lymphocytes, 17 per cent.; large mononuclear and transitional forms, 2 per cent.; and mast cells 10.5 per cent. Case 18 of von Mullern and Grossmann,[11] also reviewed by Roth is a similar case. A child 5 years old died, after a short illness, of fever with hemorrhagic tendencies, with the blood findings of an acute myelogenous leukemia. Necropsy showed subacute and acute tuberculosis of the lymph glands and myelogenous metaplasia in the spleen and liver. Roth also includes Bruchmann's[12] case in this class (tuberculosis of the lymph glands and of the peritoneum together with myelogenous leukemia in a boy 13), and Masing's (a man of 20 with "leukemia") necropsy showing tuberculous nodules in the lungs and pleura, also tuberculosis of the bronchial glands. Leube's[13] case, which gave rise to the conception of leukanemia when viewed in the light of more recent studies of the blood changes in severe infectious processes, would have to be regarded as a case of general sepsis with an unusual functional leukocytosis. His case was a boy 4 years old who died from a high fever after a short illness. There was a severe anemia (hemoglobin 10 per cent.) and a differential leukocyte count as follows: neutrophils, 44.1 per cent.; neutrophil myelocytes, 13 per cent.; eosinophils, 0.6 per cent.; large lymphocytes, 4.9 per cent.; small lymphocytes, 35.3 per cent. Necropsy showed a septic tumor of the spleen with central abscess and small abscesses in the liver.

Hertz[14] regards the majority of the reported cases of acute myelogenous leukemia as cases of severe infection. He holds that there is no uniform etiology but that various infectious centers are capable of producing such a blood picture. An unusual susceptibility on the part of the individual, no doubt, is also an important factor. This same tendency in a minor degree is a matter of common observation in various infectious processes, manifesting itself by the appearance in the blood stream of a few myelocytes. The deviation of the Arneth count to the left is a manifestation of this same tendency and while it is only a feeble manifestation, it is, nevertheless, regarded as a true expression of the ratio between the strength of the invading organism on the one hand and the resistance of the individual on the other.

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11. Von Mullern and Grossmann: Beitr. z. path. Anat. u. z. allg. Path., 1912, lii. Reviewed by Roth in Ztschr. f. klin. Med., 1913, lxxviii, 75.
12. Bruchmann: Ein Fall von Lymphdrüsen und Bauchfelltuberkulose usw., Arbeiten aus dem patholog., Anatom. Institut. zu Tübingen, ii, Part 3.
13. Leube: Sitzungsb. d. phys. med. Gesellsch., Würzburg, 1900.
14. Hertz: Die Akute Leukämie, Wein, 1911.

A study of this case and a review of similar cases in the literature leads to the conclusion that many of the so-called cases of acute leukemia are, after all, only cases of infection, presenting unusual leukocyte pictures.

The writer wishes to express his appreciation of the kindness of Dr. A. S. Warthin in contributing the very complete necropsy report.

THE URIC ACID SOLVENT POWER OF URINE CONTAINING HEXAMETHYLENAMIN (UROTROPIN) AS COMPARED WITH THAT OF NORMAL URINE*

HOWARD D. HASKINS, M.D.
PORTLAND, ORE.

It has been known for a long time that hexamethylenamin in aqueous solution has the power of putting into solution considerable uric acid. In illustration of this point we take occasion to report one of our own experiments. An excess of pure uric acid was added to five solutions of hexamethylenamin, and after being shaken they were kept in an incubator at body temperature over night. The uric acid in the filtrates from these was estimated by the usual method, the results being as follows:

35.00 mg. of uric acid dissolved by 100 c.c. of 0.1 per cent.
66.00 mg. of uric acid dissolved by 100 c.c. of 0.25 per cent.
74.00 mg. of uric acid dissolved by 100 c.c. of 0.4 per cent.
158.00 mg. of uric acid dissolved by 100 c.c. of 2.0 per cent.
250.80 mg. of uric acid dissolved by 100 c.c. of 5.0 per cent.

The solubility of uric acid in distilled water under the same conditions is about 8.4 mg. From these findings it is easy to understand how the claim could be made that hexamethylenamin exerts a marked uric acid solvent action. It is necessary, however, to mention parenthetically, that such concentrations as these are greater than can occur in the urine after administration of therapeutic doses.

When we investigate the behavior of urines containing hexamethylenamin we find that many of them possess no power to take up uric acid in addition to that already present, while, on the other hand, many do show a marked solvent power. The investigation reported in this paper has shown that those hexamethylenamin urines which possess a distinct uric acid solvent power are the ones which have the same acidity reaction as those normal urines that have the ability to dissolve uric acid in appreciable quantity. It became necessary, therefore, to make an extended study of the action of normal urines[1] in dissolving uric acid, and then to compare the results with those obtained with

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* Department of Biochemistry, Medical School, University of Oregon.

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1. It is the author's intention to give all the data for normal urine quite fully in a separate paper.

urines containing the drug. It seems quite possible that by means of this comparison the present research has settled the question of the uric acid solvent power of hexamethylenamin.

METHODS

The uric acid estimations were made by the usual method, i. e., by precipitation by means of ammonium hydroxid in the presence of a considerable concentration of ammonium sulphate, filtration and subsequent solution of the precipitate in hot dilute sulphuric acid and its estimation by titration with a standard solution of potassium permanganate.

In determining solvent power the urines were first warmed to 37 C., and after adding an excess of pure uric acid the flasks were kept in a bath at 37 C. for exactly twenty minutes, the urines being shaken frequently so that undissolved uric acid was constantly in suspension. They were filtered immediately after removal from the bath, and the uric acid estimation was made on the filtrates. A longer period of warming and shaking was not found to give superior results. Body temperature was chosen so as to be comparable to the physiological condition of urine lying in the bladder.

The hydrogen-ion concentration or acidity of the urine was determined by the method of Henderson and Palmer.[2] Without this method the research could never have been satisfactorily carried out. The figures in the tables for acidity of the urines are the "hydrogen exponents"; these are really (negative) logarithmic figures corresponding to the true hydrogen-ion concentrations. The smaller the figure the greater the acidity. Exact neutrality is 7.0. The reaction of the normal urines which we have examined ranges from a distinctly acid urine, 5.0, to a slightly alkaline urine, 7.4; never quite equalling the alkalinity of blood which is 7.45 to 7.65.

The most puzzling part of the work was to discover the factors which control the solvent action of normal urine on uric acid. The only factors which we have definitely proved to play a part are the acidity and the concentration of the urine. As to the effect of the acidity, it was found that practically all urines, 6.5 to 7.4, are able to take up additional uric acid, and that a certain proportion of more acid urines, 6.2 to 6.45, dissolve some uric acid, but very few of those, 5.8 to 6.1, have any effect. The amount of uric acid dissolved corresponds roughly to the reaction, increasing as the acidity lessens. As regards the other factor, namely, concentration of the urine, it was a surprise to find that many dilute urines dissolve a disproportionately large amount of uric acid. One might naturally suppose that a 50 per cent. dilution of a particular urine would dissolve about half as much as the undiluted urine, but as a matter of fact it dissolves much more than that. In consequence of this in the tables below dilute hexamethylenamin urines are compared with dilute normal urines, and the less dilute with less dilute controls.

We had great difficulty in securing a sufficient number of samples of urine, both normal and drug-containing, of low enough acidity to show uric acid solvent power.[3] This was especially true in summer (at which time most of the work had to be done), since on hot days almost every sample of urine passed proved to be too acid to dissolve uric acid.

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2. Henderson, L. J., and Palmer: Jour. Biol. Chem., 1913, xiii, 393.

3. The author wishes to express his indebtedness to the large number of students and others who have furnished urines for this research, but most of all to Dr. P. J. Hanzlik and R. J. Collins, who secured the samples of hospital urines as well as other urines. They also made most of the tests for hexamethylenamin. The assistance of C. J. Friedman in the research was invaluable.

It may be postulated as a necessary presupposition that in order to be able to claim that a particular urine containing hexamethylenamin dissolves more uric acid than the same urine would if it contained no hexamethylenamin, such a urine must take up distinctly more uric acid than do normal urines of corresponding acidity and concentration. Only on this basis can we determine that hexamethylenamin as actually excreted in the urine is a factor in the uric acid solvent action.

The tables give the results of the experimental work, normal urines serving as controls for comparison. The figures for uric acid are given as milligrams in 100 c.c. of urine. "Uric acid content" means the amount present in the urine as passed. "Total uric acid" means the amount present in the filtrate after shaking with uric acid. The difference betweeen these two is the "uric acid dissolved." This last is the index of the solvent power of the urine. In the half of the tables giving the controls the columns are arranged in reverse order so as to bring the figures for "uric acid dissolved" close together for ready comparison. As regards the dosage of hexamethylenamin, a single dose was taken by the normal individuals except in three instances, when two doses of 2 gm. were taken (2 x 2 in the table); in such cases the time interval for secretion of the urine was calculated from the time of taking the last dose. The dispensary patients took single doses, but the hospital patients took the drug regularly, the number of *times* per day or the *hours* between doses being indicated in the tables.

COMMENT ON THE TABLES

It may be objected by some that in a few of the cases reported above, the time interval for secretion of the urine follows too closely the administration of hexamethylenamin to allow the urine to acquire more than a trace of the drug. According to data furnished by Dr. P. J. Hanzlik, however, after giving a single dose of 2 gm. the urine gives a distinct test as early as twenty minutes in about 20 per cent. of the cases and inside of thirty-five minutes in about 75 per cent. of the cases.

On studying Table 1 we find that the uric acid solvent power of most of the drug urines is no greater than that of the controls, in some cases a few milligrams in excess; but in only two cases is there a notable excess of uric acid dissolved (namely, acidity 6.6—105 mg. and acidity 6.3—65 mg). In the first of these cases it is not certain that the solvent action is attributable to hexamethylenamin, because we have record of other controls (somewhat less dilute) which show as great solvent power (e. g., acidity 6.65—135 mg., and acidity 6.6—96 mg.). But in the other case there is probably some true solvent action of the drug, for we have never found so large an amount of

TABLE 1.—URINES CONTAINING HEXAMETHYLENAMIN—

DILUTE URINES OF NORMAL PERSONS

Acidity	Dosage gm.	Time Hours	Hexam. Test	Uric Acid Content mg.	Total Uric Acid mg.	Uric Acid Dissolved mg.
7.2	2.0	0 -1	+	31.65	178.69	147.04
7.2	2.0	0 - ¾	+	17.92	88.88	70.96
6.95	2.0	0 -6	+	8.96	77.78	68.82
....	....	.....	..	.....	.....	.....
....	....	.....	..	.....	.....	.....
6.75	2.0	1 -1¾	+	7.48	48.92	41.44
....	....	.....	..	.....	.....	.....
6.7	2.0	1¾-2¾	+	8.22	88.14	79.92
6.7	2.0	¼- ½	+	7.48	77.04	69.56
6.7	2.0	5½-6	+	8.96	68.96	59.94
6.6	2.0	2¾-4	+	8.96	114.04	105.08
6.6	2.0	4 -5	+	17.92	97.84	79.92
6.6	2.0	3¼-4	+	9.70	61.50	51.80
6.5	2.0	4 -5½	+	26.80	96.36	69.56
6.5	2.0	1 -2½	+	19.40	87.40	68.00
6.45	2.0	2½-3	+	8.96	46.70	37.74
6.45	2.0	½- ¾	+	7.48	42.26	34.78
6.45	2.0	¾-1	+	8.22	38.56	30.34
6.4	2 × 2	0 - ½	+	10.44	62.24	51.80
....	....	.....	..	.....	.....	.....
6.35	2.0	2½-3	+	9.70	34.86	25.16
6.35	2.0	¼- ½	+	7.48	32.64	25.16
6.3	2 × 2	2½-4	+	32.64	97.76	65.12
6.3	1.0	0 - ¾	+	20.88	37.16	16.28
6.3	2.0	½-1	+	7.48	31.16	23.68
6.1	2 × 2	½-2½	+	18.58	60.76	42.18
6.1	2.0	1½-2½	+	14.88	37.24	22.36
6.1	1.0	0 -2	+	9.70	33.38	23.68
5.85	2.0	1½-2	+	8.22	11.18	2.96
5.8	2.0	2¼-4	+	20.88	25.24	4.36

TABLE 2.—

LESS DILUTE URINES OF NORMAL PERSONS

7.25 *	1.0	¾-3	+	78.71	335.85	257.14
....	...	.....	..	.....	.....	.....
7.2	1.0	¾-3½	+	37.08	161.40	124.32
....	...	.....	..	.....	.....	.....
7.1	1.0	½-4½	+	43.00	176.94	133.94
....	...	.....	..	.....	.....	.....
5.95	1.0	0-3¼	+	47.52	51.88	4.36
....	...	.....	..	.....	.....	.....

TABLE 3.—

URINES OF DISPENSARY PATIENTS

7.2	2.0	¾-1¾	+	16.40	102.80	86.40
....	...	.....	..	.....	.....	.....
6.65 *	2.0	0 -1	+	18.40	87.50	69.10
....	...	.....	..	.....	.....	.....
....	...	.....	..	.....	.....	.....

—CONTROLS. URINES CONTAINING NO HEXAMETHYLENAMIN

DILUTE NORMAL URINES

Uric Acid Dissolved mg.	Total Uric Acid mg.	Uric Acid Content mg.	Acidity	Remarks
144.75	154.50	9.75	7.3	
157.29	172.25	14.96	7.1	
118.40	138.80	20.40	7.0	
105.66	122.16	16.50	6.95	
69.60	78.00	8.40	6.95	
83.00	91.25	8.25	6.75	
57.20	66.00	8.80	6.75	
96.75	105.00	8.25	6.7	
66.38	81.91	15.53	6.7	
61.50	69.00	7.50	6.7	
75.75	83.25	7.50	6.6	
74.41	78.12	3.71	6.6	
63.00	72.00	9.00	6.6	
63.92	76.16	12.24	6.5	
50.80	66.00	15.20	6.5	
51.48	59.04	7.56	6.45	
33.60	41.20	7.60	6.45	
32.80	55.60	22.80	6.45	
48.75	68.40	19.65	6.4	
31.20	38.80	7.60	6.4	
22.94	30.42	7.48	6.35	
5.60	14.00	8.40	6.35	
33.75	41.25	7.50	6.3	
19.20	31.60	12.40	6.3	
19.50	27.06	7.56	6.25	
.....	.....	.....	....	
37.91	52.33	14.42	6.0	
12.00	22.00	10.00	6.0	
14.82	25.50	10.68	5.95	
20.00	29.20	9.20	5.8	

—TABLE 2.—(*Continued*)

LESS DILUTE NORMAL URINES

350.00	446.55	96.55	7.3 *	*$NaHCO_3$ administered.
223.50	279.00	55.50	7.2 *	
188.16	250.08	61.92	7.2	
182.04	238.36	56.32	7.2	
172.00	244.40	72.40	7.1	
135.42	185.82	50.40	7.1	
8.80	34.00	25.20	6.1	
40.56	76.20	35.64	5.9	

—TABLE 3.—(*Continued*)

CONTROL URINES

188.50	231.34	42.84	7.2	
157.29	172.25	14.96	7.1	
75.80	115.00	39.20	6.7 †	† Urine of same person as *.
54.40	69.60	15.20	6.65	
66.40	93.20	26.80	6.65	

TABLE 4.—URINES CONTAINING HEXAMETHYLENAMIN—

VERY DILUTE URINES OF HOSPITAL PATIENTS

Acidity	Dosage gm.	Dosage Times	Hexam. Test	Uric Acid Content mg.	Total Uric Acid mg.	Uric Acid Dissolved mg.
7.4	1.0	4	+	4.66	22.50	17.84
6.95	1.0	4	+	5.07	46.98	41.91
...	...	..	..	.....	.....	.....
...	...	..	..	.....	.....	.....
...	...	..	..	.....	.....	.....
6.75	1.0	4	+	6.53	68.47	61.94
6.75	0.6	4	Trace	4.66	77.28	72.62
6.7	1.0	4	+	5.49	48.65	43.16
....	...	..	..	.....	.....	.....
6.65	0.6	4	+	4.66	54.46	49.80
6.45	1.0	4	+	4.24	44.91	40.67
6.45	0.6	4	+	5.08	31.80	26.72
6.4	1.0	4	+	4.85	42.22	37.37
6.4	0.6	4	+	6.32	37.86	31.54
6.35	1.0	4	+	4.20	39.40	35.20
6.35	0.6	4	+	4.20	39.00	34.80
6.35	1.0	4	+	3.80	20.20	16.40
6.35	1.0	4	+	4.20	18.20	14.00
6.35	0.6	4	+	4.20	17.80	13.60
6.3	1.0	4	+	4.60	43.00	38.40
6.3	0.6	4	+	4.66	35.37	30.71

DILUTE URINES OF HOSPITAL PATIENTS TABLE 5.—

7.15 *	0.6	5	+	10.44	189.52	179.08
7.15 *	1.0	4	+	4.25	105.92	101.67
7.0 *	1.0	4	+	13.79	117.54	103.75
6.9 *	1.0	4	+	10.05	103.01	92.96
....	...	..	..	.....	.....	.....
6.85 *	0.6	4	+	10.98	119.71	108.73
6.85 *	1.0	4	+	15.03	83.09	68.06
6.8 *	0.6	4	+	11.81	84.85	73.04
....	...	..	..	.....	.....	.....
6.75 *	0.6	5	+	16.36	80.74	64.38
6.75 *	0.6	4	+	10.98	62.44	51.46
6.5 *	0.6	5	+	13.40	69.64	56.24
....	...	..	..	.....	.....	.....
6.45 *	0.6	5	+	11.92	74.82	62.90
...	...	..	..	.....	.....	.....
6.4 *	0.6	3	+	10.15	67.42	57.27

LESS DILUTE URINES OF HOSPITAL PATIENTS TABLE 6.—

7.25 *	0.6	5	+	28.94	94.06	65.12
....	...	..	..	.....	.....	.....
6.95 *	0.6	5	+	30.42	100.72	70.30
....	...	..	..	.....	.....	.....
6.6 *	0.6	Every 2 hrs.	+	82.58	86.51	3.93
...	...	..	..	.....	.....	.....
6.35 *	0.6	Every 2 hrs.	+	82.02	95.64	13.62
6.35 *	1.0	4	+	22.60	29.00	6.40
6.3 *	0.6	Every 2 hrs.	+	95.64	99.45	3.81
....	...	..	..	.....	.....	.....

—CONTROLS. URINES CONTAINING NO HEXAMETHYLENAMIN

DILUTE URINES

Uric Acid Dissolved mg.	Total Uric Acid mg.	Uric Acid Content mg.	Acidity	Remarks
144.75	154.50	9.75	7.3	The patients were typhoid cases. *Urines from typhoid patients when taking no drug.
71.78	76.26	4.48	7.15 *	
105.66	122.16	16.50	6.95	
32.19	36.67	4.48	6.9 *	
41.07	45.55	4.48	6.85 *	
66.60	75.56	8.96	6.75	
37.74	42.59	4.85	6.75 *	
96.75	105.00	8.25	6.7	
48.00	56.40	8.40	6.7	
66.00	73.50	7.50	6.65	
61.60	72.40	10.80	6.45	
18.40	26.80	8.40	6.45	
46.95	74.90	27.95	6.4	
27.60	52.40	24.80	6.4	
22.94	30.42	7.48	6.35	
19.20	26.80	7.60	6.35	
13.60	21.20	7.60	6.35	
5.60	14.00	8.40	6.35	
.....	.....	.....	....	
33.75	41.25	7.50	6.3	
19.20	31.60	12.40	6.3	

—TABLE 5.—(*Continued*) DILUTE NORMAL URINES

144.75	154.50	9.75	7.3	* Case of pleurisy.
157.29	172.25	14.96	7.1	* Case of typhoid fever.
118.40	138.80	20.40	7.0	* Case of typhoid fever.
141.75	150.08	8.33	6.9	* Case of typhoid fever.
130.07	139.06	8.99	6.9	
136.16	144.50	8.34	6.85	* Case of pyelocystitis.
109.29	128.69	19.40	6.85	* Case of typhoid fever.
116.80	135.60	18.80	6.8	* Case of pyelocystitis.
102.20	109.68	7.48	6.8	
83.00	91.25	8.25	6.75	* Case of pleurisy.
66.60	75.56	8.96	6.75	* Case of pyelocystitis.
50.80	66.00	15.20	6.5	* Case of pleurisy.
49.58	59.28	9.70	6.5	
61.60	72.40	10.80	6.45	* Case of pleurisy.
51.48	59.04	7.56	6.45	
48.75	68.40	19.65	6.4	* Case of septicemia.

—TABLE 6.—(*Continued*) LESS DILUTE NORMAL URINES

188.50	234.34	45.84	7.2	* Case of pleurisy.
182.04	238.36	56.32	7.2	
162.40	207.60	45.20	6.95	* Case of pleurisy.
94.40	122.00	27.60	6.95	
96.79	123.60	26.81	6.6	* Case of typhoid fever.
75.48	158.52	83.04	6.6	
29.36	107.96	78.60	6.35	* Case of typhoid fever.
13.60	42.00	28.40	6.3	* Case of typhoid fever.
10.20	78.60	68.40	6.3	* Case of typhoid fever.
10.40	66.00	55.60	6.3	

uric acid dissolved by a control urine of this degree of acidity. This result is doubtless due to the fact that two doses were taken close together, amounting to almost the same thing as taking a single dose of 4 gm. (compare the results reported in Table 7).

In Table 2 the high solvent power of the first urine must be compared (as is done in the table) with urines obtained after taking a similar dose of sodium bicarbonate as was taken with the drug. In both Tables 2 and 3 there is no evidence of solvent action due to hexamethylenamin.

TABLE 7.—CONTRAST OF TESTS WITH—URINES OF NORMAL PERSONS AFTER AN EXCESSIVE DOSE OF HEXAMETHYLENAMIN

Acidity	Dosage gm.	Time Hours	Hexam. Test	Uric Acid Content mg.	Total Uric Acid mg.	Uric Acid Dissolved mg.
6.4	4.0	0-1	+ +	69.84	265.92	196.08
...	...	.....	.....	.....	.....	.....
6.0	4.0	0-2¼	+ +	44.00	262.88	218.88
6.0	4.0	0-4	+ +	61.48	209.68	148.20
5.8	4.0	0-2¼	+	72.12	79.72	7.60
5.7	4.0	0-2¼	+ +	9.80	49.32	39.52

In Tables 4, 5 and 6 only one urine (the first in Table 5, acidity 7.15) shows excess of uric acid dissolved (22 mg. above the highest control reported). But it may well be that this urine should be compared with the less dilute controls, since its specific gravity was 1.010; and among these controls we find just as great solvent power (e.g., acidity 7.1—172 mg., acidity 7.0—187 mg. and others).

In contrast with these findings the results given in Table 7 are quite striking. Four of the five persons taking the large dose of hexamethylenamin (equal to twenty-four hours medication for a patient) furnish urines which show greater solvent power than any controls of the same range of acidity. We have never found a normal urine of an acidity as great as 5.7 which has taken up *any* extra uric acid. Furthermore, the hexamethylenamin urines of acidity 6.0 and 6.4 dissolved as much uric acid as control urines of acidity 6.8 to 7.2. These urines with one previously considered (see comment on Table 1) make five urines which definitely show solvent action attributable in part to the drug, but in each of these cases the dosage was extra-therapeutic. We feel free to admit, therefore, that it is very probable that after administration of *excessive* doses of hexamethylenamin, certain portions of the urine secreted may contain a sufficient concentration of the drug

to impart to them a uric acid solvent action greater than those urines would otherwise manifest.

This finding, however, is hardly of practical therapeutic application, first, because the required dose is too large, and second, because an equal effect can be secured more cheaply and easily by administration of alkaline diuretics or sodium bicarbonate in reasonable doses. For instance, if the urine be rendered faintly alkaline (7.1 to 7.4) by taking the latter agents, solvent action such as shown in Table 8 is readily obtained.

—Excessive Amounts and with No Hexamethylenamin

Controls. Urines containing no hexamethylenamin

Uric Acid Dissolved mg.	Total Uric Acid mg.	Uric Acid Content mg.	Acidity	Remarks
48.75	68.40	19.65	6.4	
31.20	75.60	44.40	6.4	
37.92	52.33	14.41	6.0	
14.82	25.50	10.68	5.95	
40.56	76.20	35.64	5.9	
20.00	29.20	9.20	5.8	

The effect of artificially adding hexamethylenamin to normal urines was also studied and the comparison made of the amount of uric acid dissolved with that taken up by the untreated urine. In most cases the drug was added in such quantity as to give a concentration of 0.05 per cent., since this was considered the greatest amount that could occur in the urine following therapeutic dosage. The acidity of the urine was unaffected by the drug. The results are given in Table 9.

It is evident that the hexamethylenamin which was added has had little if any effect, since some of the urines show a few milligrams decrease and others a few milligrams increase, but in no case a marked increase even when 0.35 per cent. of the drug is present.

As a final experiment, mixtures of monosodium and disodium phosphate solutions of concentrations similar to that of the phosphates in urines were tested as to their ability to take up uric acid both with and without added hexamethylenamin. These phosphate mixtures are quite similar to the normal urinary constituents which are most concerned in producing the hydrogen-ion concentration of urine. The results are as shown in Table 10.

TABLE 8.—Solvent Action of Alkaline Urines

Acidity	Uric Acid Content	Total Uric Acid	Uric Acid Dissolved
7.3	96.55	446.55	350.00
7.3	105.00	360.75	255.75
7.3	70.50	283.87	213.37
7.3	129.24	313.85	184.61
7.25	56.00	227.20	171.20
7.25	72.00	222.26	150.26
7.2	55.50	279.00	223.50
7.2	52.02	218.94	166.92
7.15	27.00	210.41	183.41
7.1	30.57	197.88	167.31

TABLE 9.—Effect of Adding Hexamethylenamin to Normal Urines

Acidity	Controls Uric Acid Dissolved (No Hexam.)	Uric Acid Dissolved (Hexam. Added)	Hexam. Per Cent.
7.2	188.492	204.750	0.05
7.2	85.800	75.660	0.05
6.9	101.833	94.250	0.05
6.8	79.167	100.000	0.05
6.7	46.250	42.550	0.35
6.7	67.340	85.840	0.35
6.5	63.917	58.500	0.05
6.0	39.008	47.675	0.05

TABLE 10.—Solvent Action of Phosphate Solutions

Acidity	Controls Phosphate Without Hexam. Uric Acid Dissolved	Phosphate With Hexam. Uric Acid Dissolved	Hexam. Per Cent.
7.15	154.00	155.60	0.05
6.8	102.00	105.20	0.05
6.25	26.80	28.00	0.05
7.15	154.00	147.60	0.1
6.8	102.00	108.40	0.1
6.25	26.80	31.60	0.1
6.8	61.20	81.20	1.0
6.65	38.80	74.00	1.0
6.45	32.40	62.00	1.0

The first two sections of the table show no dissolving power in excess of the controls, but the last section shows distinct and uniform solvent action attributable to the drug. Thus, as in the case of urine, we find that it is simply a question of the concentration of the hexamethylenamin; ordinary concentrations giving rise to no solvent action, but excessive concentrations causing solvent action.

Undoubtedly the reason why the stronger solutions show more distinct solvent action is because a greater amount of formaldehyd is set free than in weaker solutions, and it is the formaldehyd that causes solution of the uric acid. In neutral or slightly alkaline solutions formaldehyd is not set free from hexamethylenamin. Ordinary distilled water is sufficiently acid (due to CO_2) to induce the reaction. Hanzlik[4] found no formaldehyd in urines of acidity 7.0 to 7.4 after administration of hexamethylenamin, but found it in almost every urine which was truly acid, 4.85 to 6.95. We found that a 1 per cent. solution of the drug in a phosphate mixture of an acidity 7.2 dissolves a smaller amount of extra uric acid than does a 1 per cent. solution in a phosphate mixture of the same concentration (1/30 gm. molecular) but of greater acidity, 6.8.

TABLE 11.—Comparison with Effect of Phosphate Mixture

Acidity	Control Phosphate Mixture Uric Acid Dissolved	Phosphate with Hexam. Uric Acid Dissolved	Extra Uric Acid Dissolved	Hexam. Per Cent.
7.2	173.24	204.32	31.08	2.0
7.2	173.24	186.56	13.32	1.0
6.8	100.81	121.57	20.76	1.0

The question may be asked, why does the hexamethylenamin dissolve *any* extra uric acid in the alkaline mixture (7.2)? The answer is found in the fact that the acidity of the solution gradually changes as uric acid is taken up. The filtrate from the 7.2 control after shaking with uric acid had an acidity of 6.8. In consequence of this, formaldehyd was finally liberated in the hexamethylenamin phosphate solution (and dissolved extra uric acid), whereas in the more acid phosphate solution (6.8) formaldehyd was being liberated during the entire time of the shaking. It will be noticed in Table 11 that the 2 per cent. solution has the greatest effect, the shorter time for liberation

4. Hanzlik, P. J., and Collins, R. J.: The Archives Int. Med., 1913, xii, 578.

of formaldehyd (as compared with the solution of acidity 6.8) being more than compensated for by the greater concentration of the drug.

CONCLUSIONS

1. In the case of urines hexamethylenamin exerts a uric acid solvent action only after the administration of excessive doses.

2. Alkaline diuretics impart to the urine as great solvent power as these excess doses of hexamethylenamin.

761 Lovejoy Street.

AN OXYDASE REACTION ON BLOOD SMEARS

A VALUABLE TEST IN THE IDENTIFICATION OF WHITE BLOOD CELLS OF UNCERTAIN ORIGIN *

FRANK A. EVANS, M.D.
Resident Medical House Officer The Johns Hopkins Hospital
BALTIMORE

In view of the uncertainty that exists as to the origin and status of many white cells of the blood and the difficulty in differentiating between some cells of myeloid and lymphoid origin such as the Naegeli myeloblast and the pathological lymphocyte, any procedure that affords additional information on this subject is of value. The demonstration of the content of any cell in oxydase ferments affords a biological reaction that is of great help, inasmuch as it has been shown that cells of myeloid origin contain such ferments and those of lymphoid origin do not. This difference was first definitely noted by Meyer[1] in 1903, who, following on the observation of Brandenburg[2] in 1900, that the blood in myeloid leukemia frequently gave a positive guaiac reaction without the presence of peroxid or turpentine, found that with this test granules of oxydase ferment could be demonstrated in the granulocyte cells of the blood but not in the lymphocytes. Later Winkler[3] devised another and more reliable method based on the "indophenolblau" synthesis of Ehrlich[4] (alpha-naphthol and dimethyl-paraphenylendiamin with one atom of oxygen form a white substance and with another blue "indophenolblau"), and demonstrated with this the oxydase granules in gonococcus pus and in leukocytes in the tissues, but not in lymphocytes.[5] This he suggested as a convenient method of proving inflammation in the appendix and other lymphoid tissue and predicted the coming usefulness of the test in the study

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* From The Clinical Laboratory of the Medical Clinic of The Johns Hopkins Hospital.

1. Meyer, E.: Beiträge zur Leukocytenfrage, München. med. Wchschr., 1903, L-ii, 1489.

2. Brandenburg, K.: Ueber die Reaktion der Leukocyten auf die Guaiaktinctur, München. med. Wchnschr., 1900, xlvii-i, 183.

3. Winkler, F.: Der Nachweis von Oxydase in den Leukozyten mittels der Dimethylparaphenylendiaminalphanaphtholreaktion, Folia Haemat., 1907, iv, 323.

4. Ehrlich, P.: Das Sauerstoffbedürfnis des Organismus, p. 92, Berlin 1885, August Hirschwald.

5. Winkler, F.: Die Oxydasereaktion im gonorrhoischen Eiter, Folia Haemat., 1908, v-vi, 17.

of the origin of the different white blood cells. It is the reliability of this test and the possibilities that lie in its application to blood smears, and a technic for the same, that form the discussion in this paper.

Schultze[6] submitted many body tissues to this "indophenolblau" reaction after formaldehyd fixation and found the oxydase granules in the tear and thyroid glands in addition to cells of myeloid origin. He, however, found these granules in no other body cells and used the test in the differential diagnosis of the leukemias. This work has been repeated by several others with similar results.[7] Schultze later modified his technic[8] by using sodium betanaphthol (Mikrozidine-Merck) and dimethylparaphenylendiamin hydrochlorid. With this the oxydase granules become a light green, and later, after treatment with water, a violet-black; and the fat droplets and lipoid substances stain a reddish color that is to be distinguished from that of the oxydase granules. Gierke[9] by the original "indophenolblau" synthesis brought the granules out in many body cells in fresh tissue but obtained results similar to those of Schultze after formaldehyd fixation and with an alkaline solution of the alphanaphthol which he used. To explain this phenomenon Gierke presents the hypothesis that the reaction on fresh tissue depends on the labile respiratory oxygenase, a peroxydase reaction, destroyed or inactivated by the formaldehyd fixation used by Schultze, whereas the more stabile oxydase of the myeloid cells endures. Kreibich[10] speaks of the reaction in the myeloid cells also as a peroxydase reaction but believes it is specific for the myeloid cells. By treating the material with a 1 to 2 per cent. solution of benzidin monosodium-sulphate to which 2 to 3 drops of 30 per cent. perhydrol has been added, he claimed to obtain a preparation that demonstrated the peroxydases in only the granulocyte cells, and which resisted alcohol, xylol and balsam and might be counterstained with Loeffler's methylene blue, eosin or Ehrlich's stain. The "indophenolblau" oxydase reaction is of very short duration and counterstaining is difficult; so any such method as suggested by Kreibich for a permanent preparation that admits of staining is a great advantage. But so far his claims for the specificity of this peroxydase reaction have not been

6 Schultze, W.: Zur Differentialdiagnose der Leukämieen, München. med. Wchnschr., 1909, lvi, 167.

7. See Türk, W.: Vorlesungen über Klinische Haematologie, p. 202, Wien und Leipzig, 1912, Wilhelm Braumüller.

8. Schultze, W.: Weitere Mittellungen über Oxydasereaktionem an Gewebsschnitten, München. med. Wchnschr., 1910, lvii-ii, 2171.

9. Gierke, E.: Die Oxydierenden Zellfermente, München. med. Wchnschr., 1911, lviii-ii, 2315.

10. Kreibich, C.: Ueber Oxydasen and Peroxydasen, Wien. klin. Wchnschr., 1910, xxiii, 1443.

substantiated. Klopfer[11] by the "indophenolblau" synthesis after formaldehyd fixation, found the oxydase granules only in the tear and thyroid glands and in the cells of myeloid origin, as did both Schultze and Gierke, and agreed with Gierke that the differentiation between a labile and stabile ferment by formaldehyd fixation is sharp. Dietrich[12] maintained that the "indophenolblau" is a fat stain and that the oxidation is brought about by the general tissue metabolism, and then the fat droplets and lipoid substances take up the stain. Gierke[9] refuted this idea by showing that no granules appear after killing the ferments and adding the already oxidized solutions; and that granules still give the reaction after killing the cell life by chloroform but preserving the oxydases. However, the fat droplets in tissues are stained in the presence of the solutions used in the "indophenolblau" synthesis but they become a red-violet color, as noted by Schultze[8] and Klopfer,[11] which is readily distinguished from the blue-black "indophenolblau" of the oxydase reaction. Recently Loele[13] suggested the use of alpha-naphthol and gentian violet for the demonstration of these granules, whereby a permanent preparation may be obtained. But this, as he admits, is not an oxydase reaction and in common with the peroxydase method of Kreibich[10] needs further study as to its specificity before it may be adopted as a reliable test.[14]

That the demonstration of the presence or absence of oxydase granules by the "indophenolblau" reaction after formaldehyd fixation is trustworthy in the differentiation of cells of myeloid and lymphoid origin seems well established. As such it is useful in making the diagnosis of the type of leukemia, and especially in that large cell variety of acute lymphatic leukemia which is so difficult on morphological and tinctorial grounds alone. The reaction is also of great help in the study of white blood cells of uncertain identity and in researches on cells whose origin is not yet established.

The test, therefore, seems to be of definite clinical and experimental value, and since no detailed method for blood smears is available in the literature, it was thought that the one here devised and found reliable and convenient in the study of many different white blood cell types might prove helpful.

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11. Klopfer, A.: Experimentelle Untersuchungen über die W. H. Schultze'sche Oxydasereaktion, Ztschr. f. Exper. Path. u. Therap., 1912, xi, 467.

12. Dietrich, A.: Naphtholblausynthesis und Lipoidfärbung, Centralbl. f. allg. Path. u. path. Anat., 1908, p. 3.

13. Loele, W.: Bemerkungen zur Oxydasereaktion, Folia Haemat., 1914, xviii, 581.

14. For discussion of the various modifications of the indophenolblau oxydase reaction see Nakano, J.: Beiträge zur Kenntnis der histologischen Oxydasereaktion, der Supravital- und Vitalfärbung, Folia Haemat., 1913, xv, 123.

TECHNIC FOR BLOOD SMEARS

The technic on blood smears is necessarily somewhat more exact than on smears of pus and on tissue sections. The reliable identification of the cells containing oxydase granules demands that the smear be preserved by satisfactory fixation and that some method of counterstaining be available whereby the different nuclei may be recognized. In any technic the labile character of the ferment granules and the short duration of the "indophenolblau" reaction is to be considered. The methods suggested by Kreibich,[10] Loele[13] and others[14] for obtaining permanent preparations that demonstrate a difference in ferment content of the lymphoid and myeloid cells, have not yet been proved sufficiently reliable to admit of general adoption. The age of the smear is of importance too, for although tissue sections are said to give the reaction when a year old,[9] blood smears in this laboratory failed to give the usual reaction when over six weeks old. Fresh smears should be used whenever possible.

A. Fixation.—The usual fixing methods employed kill the ferments and are therefore forbidden. Alcohol is said not to injure the oxydases and is advised by some; but in this laboratory immersion for five minutes in absolute methyl or ethyl alcohol failed to give reliable fixation without injuring the ferments; and furthermore, that the test be specific as shown by Gierke[6] and Klopfer,[11] formaldehyd solution must be used in some form. Immersion for short periods in Formol-Müller solution or in 40 per cent. solution of formaldehyd and exposure to formaldehyd vapor has been used successfully on tissue sections. On blood smears, however, Formol-Müller solution and formaldehyd solution in various strengths were found to be mutilating and were therefore discarded. Formaldehyd vapor was entirely satisfactory, and using a 10 per cent. solution of the formalin (40 per cent. formaldehyd gas), an exposure to this in a closed jar for six to eight hours fixed all smears and injured none, although three hours fixed some and twenty-four hours did not injure others. An exposure to stronger solutions for shorter periods is not advisable, but a 25 per cent. solution for one to two and one-half hours may be used. The vapor of undiluted formaldehyd fixes the smears in a closed jar in ten minutes but weakens the oxydase reaction in such a way that, although most polymorphonuclear cells still show the granules, many myeloblasts, myelocytes, and so-called transitional cells do not.

B. Staining.—In staining, aqueous solutions used without a mordant are necessary, for the stains also must be of such composition that the ferments are not injured by them. The Romanowski stains and Ehrlich stain are forbidden by reason of the alcohol and heat, respectively, used in the technic. The blue nuclear stains do not give sharp differentiation. Aqueous gentian-violet and Giemsa stain are washed out by the aqueous solution of alpha-naphthol and dimethylparaphenylendiamin used in the subsequent "indophenolblau" synthesis too rapidly to be of any value. Saturated aqueous vesuvin and the vesuvin synthesis of Unna by means of metadiamin and sodium nitrite, suggested by Winkler[8] for differentiating nuclei and bacteria in smears of pus, stained the nuclei too faintly to be useful for blood smears. All the red nuclear stains were tried in aqueous solution and lithium carmine as used by Gierke[6] on tissue sections. Of these, only saturated aqueous safranin and 2 per cent. aqueous pyronin gave the desired intensity of staining in a short time. With either of these solutions the fixed smear is covered for eight minutes, is washed quickly and dried immediately by careful blotting. By this method the red cells and other elements remain unstained and the nuclei become an intense orange-pink that readily admits of the identification of the cell.

The staining must be done before the oxydase reaction for, if the oxydase reaction is done first, during the eight minutes consumed in staining the nuclei the "indophenolblau" has in large part faded out of many of the granules. In

some instances, when the cell type under investigation in regard to its oxydase content predominates in the smear and is readily recognized, as in the acute leukemias, the stain may be omitted.

C. The Oxydase Reaction.—Solutions: 1. One per cent. aqueous solution of dimethylparaphenylendiamin. This is a translucent, dark-purple solution when freshly made up, but later gets cloudy. It is supposed to be efficacious for only eight to fourteen days,[7] but here it was found to react well at the end of three weeks.

2. One per cent. aqueous solution of alphanaphthol dissolved by gentle heating; or preferably, 1 per cent. solution of alphanaphthol in 1 per cent. KOH. In this alkaline solution very little heating is necessary to bring about complete solution of the alphanaphthol. When fresh this should be a clear solution with a very faint brownish tinge. It rapidly becomes a deeper brown and is of no value at the end of the fourth day.

Procedure: Put one drop of Solution 1 and one drop of Solution 2 on a slide (a dirty, milky fluid resulting) and mount the smear, fixed, or fixed and stained according to the technic above outlined, in this and examine at once. Immediate examination is essential, for the nuclear stain endures only a few minutes in such intensity that definite identification of the cells may be made. If possible, before the oxydase reaction has become complete, locate a cell that is to be tested for oxydase granules. At first there is a very faint, diffuse blue of the protoplasm. Then small granules and finally many coarse blue-black granules appear, usually confined entirely to the protoplasm but occasionally seen to overlie the nucleus. The granules in the mature cells are frequently coarser than those in the immature ones. The height of the reaction is reached in about two minutes and endures about ten minutes. Another convenient procedure is to mount the stained smear on a slide film side upward and examine with the low or high dry objective till a field containing cells to be tested is located. The slide is then clamped down and the solutions added directly on the cover slip. With the low power objective the progress of the oxydase reaction in the cells may be watched and when it has reached its height (in about two minutes) the cover slip is carefully blotted and the field can then be examined with the high dry objective. Dry and in the air the oxydase reaction endures in its original intensity for from twenty to thirty minutes.

No satisfactory medium for mounting the preparation has as yet been found.[14] Xylol, balsam, and cedar oil quickly destroy the "indophenolblau" oxydase reaction. Winkler[8] used a solution of benzol and colophonium in equal parts for tissue sections and smears of pus, but this did not prove satisfactory for blood smears.

Summary

1. Use blood smears as fresh as possible, and certainly not more than six weeks old.

2. Fix six to eight hours in the vapor of 4 per cent. formaldehyd solution in a closed jar.

3. Stain eight minutes in a saturated aqueous safranin or a 2 per cent. aqueous pyronin solution; wash, and dry immediately.

4. Examine the smear and become familiar with the appearance of the various cell types with the nuclei thus stained.

5. (a) Put one drop of Solution 1 (less than three weeks old) and one drop of Solution 2 (less than four days old) on a slide, mount the smear in this and examine at once; or

(b) Mount the smear film side upward on a slide and put Solutions 1 and 2 directly on the smear, watch the reaction with the low power objective progress to its height, and at the end of two minutes dry and examine with the high dry objective.

The above procedure has been found a convenient and reliable method on blood smears for demonstrating the presence or absence of oxydase granules in many varieties of white blood cells, and by reason of the differentiation between cells of myeloid and lymphoid origin made possible, gives a preparation that is of great value in determining the status and origin of white blood cells of uncertain identity.

BOOK REVIEW

INFECTION, IMMUNITY AND SPECIFIC THERAPY. By John A. Kolmer, M.D., Dr.P.H., Instructor of Experimental Pathology, University of Pennsylvania.

This pretentious volume of 900 pages consists of (1) a comprehensive review of the theory of infection and immunity; (2) detailed descriptions of serological tests and the methods of vaccine and serum therapy.

The author has gone to great pains to be explicit in describing laboratory methods, and in this respect the book will be a valuable addition to the comparatively small number of laboratory manuals which have been written in English.

The technic of performing the various biological tests is given step by step, in such a way that any one trained in serological work can readily perform them. Complement fixation methods, for example, are described at length, not only for syphilis and gonorrhea, but for other infections. Vaccine therapy (including tuberculin) receives only twenty-five pages, which appears rather meager in a treatise of this kind. The book contains many illustrations, most of which serve to demonstrate some point in technic.

Dr. Kolmer's style is simple and lucid and there are very few inaccuracies; the most noticeable is the statement that a positive Wassermann rarely appears before the seventh or eighth week after a syphilitic infection.

In the discussion of tests preliminary to transfusion, there should also be some reference to the isoagglutinin and isohemolysin groups which have been studied by Moss, Ottenberg and others.

Dr. Kolmer's book is a valuable contribution to the subject and will no doubt meet with considerable popularity, especially among laboratory workers.

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